

Emergency Dermatology

Second Edition



Edited by
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Jennifer L. Parish



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Preface

Many physicians and patients do not believe that dermatology involves life-threatening situations; however, there are many emergencies that the dermatologist needs to address, and many cutaneous diseases in the emergency room that require rapid dermatologic consultation. The dermatologist is frequently the first physician to examine such patients before a hospital admission and also the first to identify a critical situation, stabilize the patient, and choose urgent and appropriate intervention. The first chapters of this book are directed toward those dermatologists who care for hospitalized patients with severe and dangerous skin diseases. Later chapters are intended for all physicians, including dermatologists, who wish to hone their diagnostic skills, expand their knowledge and understanding of pathologic events, and learn treatment options available for acute life-threatening skin diseases. This book brings together top dermatologists from around the world to address the complicated and multifaceted field of dermatologic emergencies for both the practicing dermatologist and emergency physician.

The second edition provides information and concepts that have appeared since the initial publication of *Emergency Dermatology*. New illustrations have been added, and significant references have been updated.

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Cell injury and cell death

Adone Baroni, Eleonora Ruocco, Maria Antonietta Tufano, and Elisabetta Buommino

When cells are damaged, as often occurs during trauma and metabolic stress, the organism has to choose whether to repair the damage by promoting cell survival or to remove irreparably injured cells. Cell injury occurs when an adverse stimulus reversibly disrupts the normal, complex homeostatic balance of the cellular metabolism. In this case, after injury the cells attempt to seal breaks in their membranes, chaperone the removal or refolding of altered proteins, and repair damaged DNA. On the contrary, when cell injury is too extensive to permit reparative responses, the cell reaches a “point of no return,” and the irreversible injury culminates in programmed cell death (PCD). Specific properties or features of cells make them more or less vulnerable to external stimuli, thus determining the kind of cellular response. In addition, the characteristics of the injury (type of injury, exposure time, or severity) will affect the extent of the damage.

We present a short overview of the best-known PCD pathways. We emphasize the apoptotic pathway, considered for years the hallmark of PCD, and the different stimuli that produce cell injury.

CELL INJURY

The survival of multicellular organisms depends on the function of a diverse set of differentiated cell types. After development is complete, the viability of the organism depends on the maintenance and renewal of these diverse lineages. Within each lineage homeostasis is maintained through a delicate balance between cell proliferation and cell death.¹ Disorders of either process have pathologic consequences and can lead to disturbed embryogenesis, neurodegenerative diseases, or the development of cancer²; therefore, the equilibrium between life and death is tightly controlled, and faulty elements can effectively be eliminated by PCD, a term that well defines the planned sequence of physiological cellular autodestruction, which requires both energy expenditure and a specific enzymatic network. Cell death is an essential strategy for the control of the dynamic balance of the living system, and it is the ultimate result of most physiological as well as pathological processes. Skulachev aptly described the concept of cell death using the metaphor of the “Samurai law of biology” (i.e., it is better to die than be wrong), showing that the suicide program is a way to purify cells of damaged organelles and tissues of unwanted cells that use up valuable substrates and nutrients.^{3,4} Cell death thus appears as the unique solution to eliminate what is unwanted or dangerous to the “community.”^{3,5}

In the past, PCD was mainly associated with apoptosis, a death process characterized by morphologic changes such as shrinkage of the cell, condensation of chromatin, and disintegration of the cell into small fragments (so-called “apoptotic

bodies”) that are removed by phagocytosis. On the contrary, necrosis was considered as an alternative passive cell death occurring in an accidental, violent, or chaotic way.⁶ Necrosis, however, has been recognized as a specific form of cell death with distinct morphological features.^{7,8} It is now known that cell death cannot readily be classified as “apoptosis” or “necrosis,” and alternative types of PCD have been described.^{9–11} Different PCD pathways exist, either mediated by caspases (a specific family of cysteine proteases, as in apoptosis) or caspase-independent (such as autophagic cell death [ACD], paraptosis, and programmed necrosis).¹ Death patterns may overlap or integrate, reflecting the high flexibility in cell responses to various circumstances and stimuli (Figure 1.1).

Cell injury occurs as a result of physical, chemical, or biologic insults or as a result of vital substrate deficiency. The cellular response to injury can be adaptive, when it is designed to restore homeostasis and protect the cell from further injury. In this context, the gene transcription activity is modified in favor of vital genes.⁵ If the genetic and metabolic adaptive responses are inadequate for a given injury, or if injury accumulation reaches a critical level, the damaged cells commit suicide.³ Cell injury can, therefore, be reversible (sublethal) or irreversible (lethal). Cells may be reversibly injured, but if severely injured, they may be unable to recover and cell death will occur. The death stimuli are diverse and include normal physiologic signals, such as hormones that trigger deletion of cells during differentiation or involution of tissues and organs, maturation of organ systems as, for example, in the immune system, and removal of cells that have sustained some form of damage.² Alternatively, cells already may be primed to undergo cell death, with the withdrawal of important extracellular components, such as serum or growth factors, providing the signal.¹² Other death stimuli also are important from a biomedical perspective. These include physical (ultraviolet [UV] light causing damage to the skin, hyperthermia, cold, and trauma), cytotoxic drugs, calcium agents influx, glucocorticoids, infectious agents (bacteria, virus, yeast), and hypoxia. The stimuli that initiate the death pathways vary widely with the affected cells.¹³ In particular, various stimuli (e.g., cytokines, heat, irradiation, pathogens) can cause both apoptosis and necrosis in the same cell population (Figure 1.1). Apoptosis can be induced by a lower concentration or level of almost all the stimuli that cause necrosis.¹⁴ This means that the mechanism of self-destruction can be activated by a relatively mild stimulus. Whereas mild hypoxia produced symptoms of apoptosis, severe hypoxia produced infarction and necrosis¹⁵; similarly, exposure to temperatures between 37°C and 43°C induced apoptosis in lymphocytes, and exposure to higher temperatures induced necrosis.¹⁶ Therefore, the character of the injury will determine the pattern of cell death evoked. The three main features of injury are type of injury, exposure time, and severity.

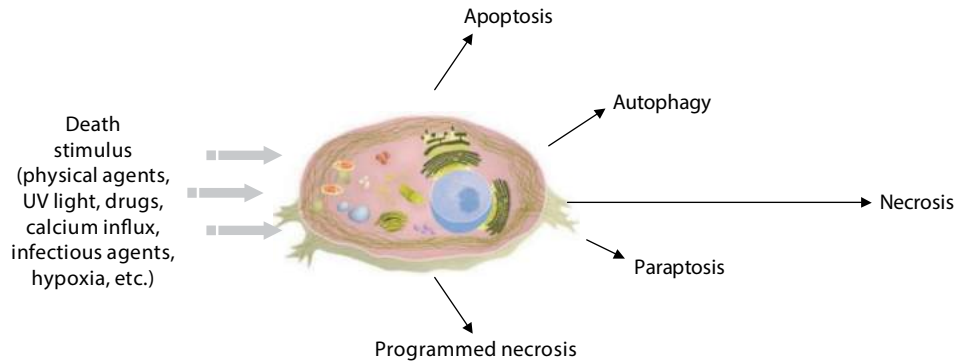


Figure 1.1 Various models of cell death. (Artwork courtesy of www.cellsalive.com.)

Type of Injury

The injury can be, for example, physical, chemical, or toxic, but the response will be different for different cell types. In fact, some cells will be more susceptible than others to agents (heart muscle cells are more susceptible than connective tissue cells to oxygen depletion).

Exposure Time

The length of exposure to a particular stimulus will affect the chances of cell survival. Relatively resistant cells will be damaged if the duration of exposure is prolonged.

Severity

The ability of a cell to survive an injury also will depend on its severity; if the withdrawal of growth factor is partial, the cell is still able to survive for a long period (depending on cellular resistance), but if it is complete, cell death occurs in a very short time with modalities that vary from cell to cell.

We now describe some models of cellular death, taking into consideration that a clear-cut definition cannot be given due to the overlapping of the different programs of cell death.

Apoptosis

Cells have different ways of committing suicide and may select the fastest and most effective of the options available. Apoptosis has been considered for years as the PCD paradigm and is still considered one of the main pathways activated during stressful conditions. The term “apoptosis” derives from the ancient Greek word used to describe the “falling off” or “dropping off” of petals from flowers or leaves from trees, to emphasize the normal physiological nature of the process.¹⁷ As part of the immune response, apoptosis allows the elimination of virally infected and cancer cells or the deletion of unnecessary or potentially dangerous lymphocytes.¹⁸ Defects of apoptotic cell death may promote tumor or autoimmune disease development. The apoptotic process has been shown to proceed via a number of discrete steps. Cells undergoing apoptosis are characterized morphologically by cell shrinkage, chromatin condensation, loss of contact with neighboring cells and the extracellular matrix (Figure 1.2),¹⁹ actin cleavage,²⁰ and biochemically by DNA laddering (Figure 1.3).¹⁹ The last is a peculiarity of most apoptotic pathways. The double-stranded linker deoxyribonucleic acid (DNA) between nucleosomes is cleaved

at regularly spaced internucleosomal sites, giving rise to DNA fragments representing the length of nucleosomes (180–200 base pairs).¹³ Molecular characterization of this process identifies a specific DNase (caspase-activated DNase) that cleaves chromosomal DNA in a caspase-dependent manner.²¹ Other features of apoptosis are early depolymerization of cytoskeletal proteins, loss of phospholipid symmetry in the plasma membrane with the outer layer exposure of phosphatidylserine (PS) residues, and the appearance of a smooth-surfaced protuberance of the plasma membrane with its preserved integrity. The fragmentation of both nucleus and whole cell then produces membrane-bound bodies in which the organelles are intact to form apoptotic bodies (Figure 1.2 [inset]).²² This is also called the “budding phenomenon” and should not be confused with blebs, fluid-filled structures typically devoid of organelles.⁶ The apoptotic bodies are cleared from tissues by professional phagocytes, such as macrophages, but also epithelial cells and even fibroblasts have been shown to clear apoptotic bodies.²³ Phagocytosis is initiated by the exposure of the PS receptor located on the membrane of the phagocytes and vitronectin receptors, resulting in a cell-signaling response.²² The apoptotic pathway and the engulfment process are part of a continuum that helps ensure the noninflammatory nature of this death paradigm.²³

The suppression of proinflammatory factors, during apoptotic body clearance, is accomplished at least in part by the release of antiinflammatory factors, such as transforming growth factor β and IL-10, by macrophages engaged in corpse engulfment. Regulatory mechanisms help ensure that, when phagocytosing dendritic cells present peptides from apoptotic bodies to T cells, no immune reaction against self-peptides is initiated. Defects in the clearance of corpses may predispose to autoimmune disorders.

A cascade of genes is activated as a consequence of the induction of a defined genetic program in which caspases have a prominent role. Caspases are cysteine proteases (preexisting as inactive zymogen precursors in the cell) that cleave substrates at critical aspartic acid residues.¹⁸ Activation of caspases is the central event in apoptosis, leading to the cleavage of numerous proteins involved in the cell structure, cell-cycle control, and DNA synthesis and repair. The initiator caspases (caspase-2, -8, -9, and -10) are activated by interaction with caspase adapters, whereas the effector caspases (caspase-3, -6, and -7) are downstream of the activator caspases and act to cleave various cellular targets and substrates and

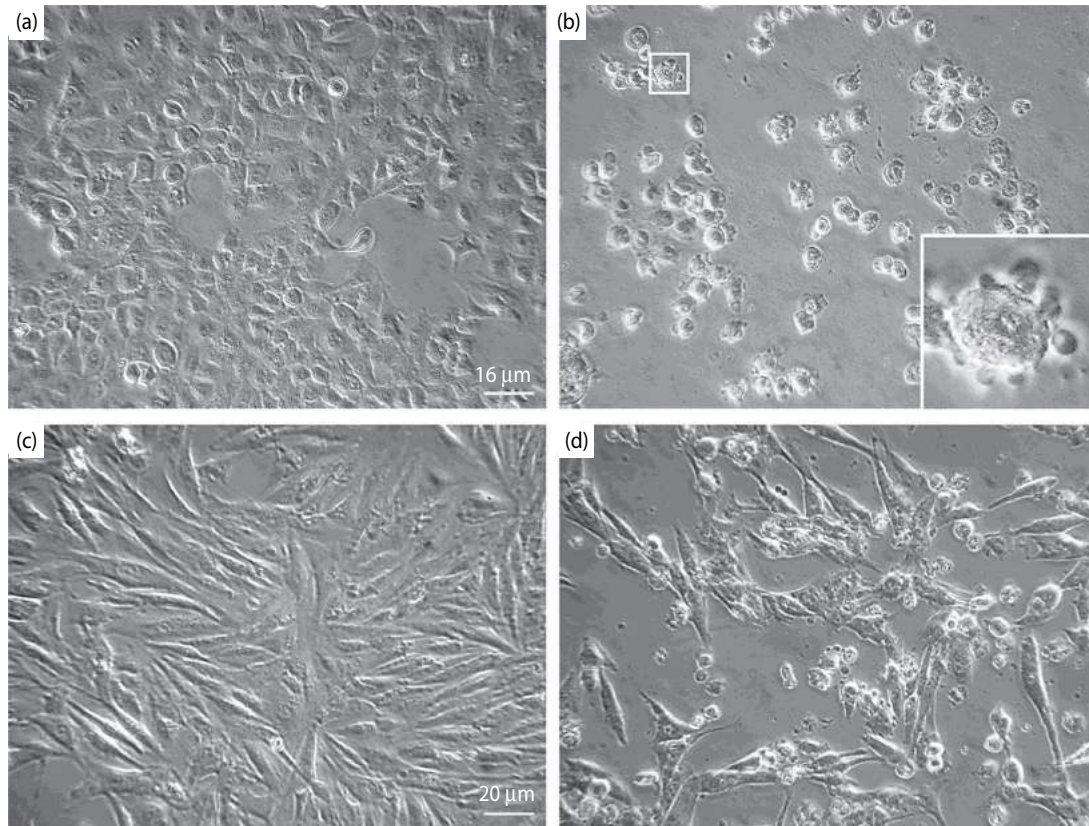


Figure 1.2 (a and c) Morphology of A549 and NCI untreated cells, respectively. Magnification: 20X. (b) Morphological changes occurring in A549 (human carcinoma lung cell line), with membrane budding shown in inset and (d) NCI (human mesothelioma cell line) cells treated with proapoptotic metabolites. ([b] From Nicoletti, R. et al., *World J Microbiol Biotechnol*, 2008;24:189–195; [d] from Buommino, E. et al., *Cell Prolif*, 2010;43:114–123.)

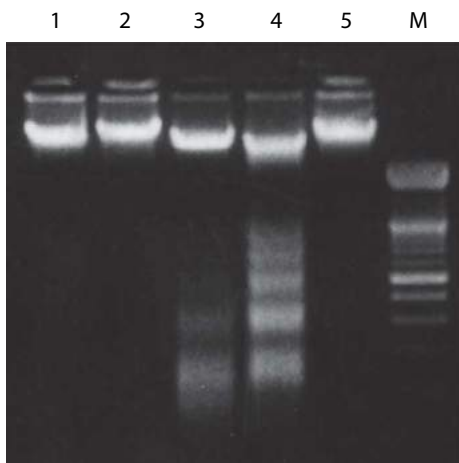


Figure 1.3 DNA feature of HeLa cells treated or not with 3-O-methylfunicone. DNA fragmentation induced in OMF treated cells after 48 and 72 h (lane 3 and 4, respectively). Lane 1, untreated cells; lane 2, cells treated for 24 h; lane 5, negative control (absolute ethanol). M, 100 bp ladder (Roche Diagnostics) used as MW-marker. (From Buommino, E. et al., *Cell Prolif*, 2004; 37:413–426.)

induce cell death.¹⁸ The enzyme poly(adenosine diphosphate [ADP]-ribose) polymerase, or PARP, was one of the first proteins identified as a substrate for caspases. PARP is involved in the repair of DNA damage. It functions by catalyzing the synthesis of PARP and by binding to the DNA strand breaks and modifying nuclear proteins.²⁴ The ability of PARP to repair DNA damage is prevented following cleavage of PARP by caspase-3. The inflammatory caspases are involved in cytokine activation and are represented by caspases-1, -4, -5, -11, -12, -13, and -14.

Caspases can be activated through three main pathways: an “extrinsic” death receptor (DR)-mediated process and two “intrinsic pathways,” a mitochondria-mediated- and an endoplasmic reticulum (ER)-mediated pathway (Figure 1.4).^{1,18}

The extrinsic pathway involves the surface DRs, a subfamily of the tumor necrosis factor receptor (TNF-R) superfamily activated in response to specific extracellular signals.²⁵ To date, eight DRs have been identified, namely, Fas (CD95, Apo-1), TNF-related apoptosis-inducing ligand (TRAIL)-receptors 1 (TRAIL-R1) (DR4) and 2 (DR5, Apo-2), TNF-R1, TRAMP (WSL-1, Apo-3), EDAR, p75 neurotrophin receptor (p75NTR), and DR6.²⁵ Despite their name, not all of these receptors induce apoptosis, but they may trigger specific signaling pathways that result in a variety of cellular outcomes. The DRs comprise three domains: an extracellular cysteine-rich domain for ligand binding, a transmembrane domain, and an intracellular death domain

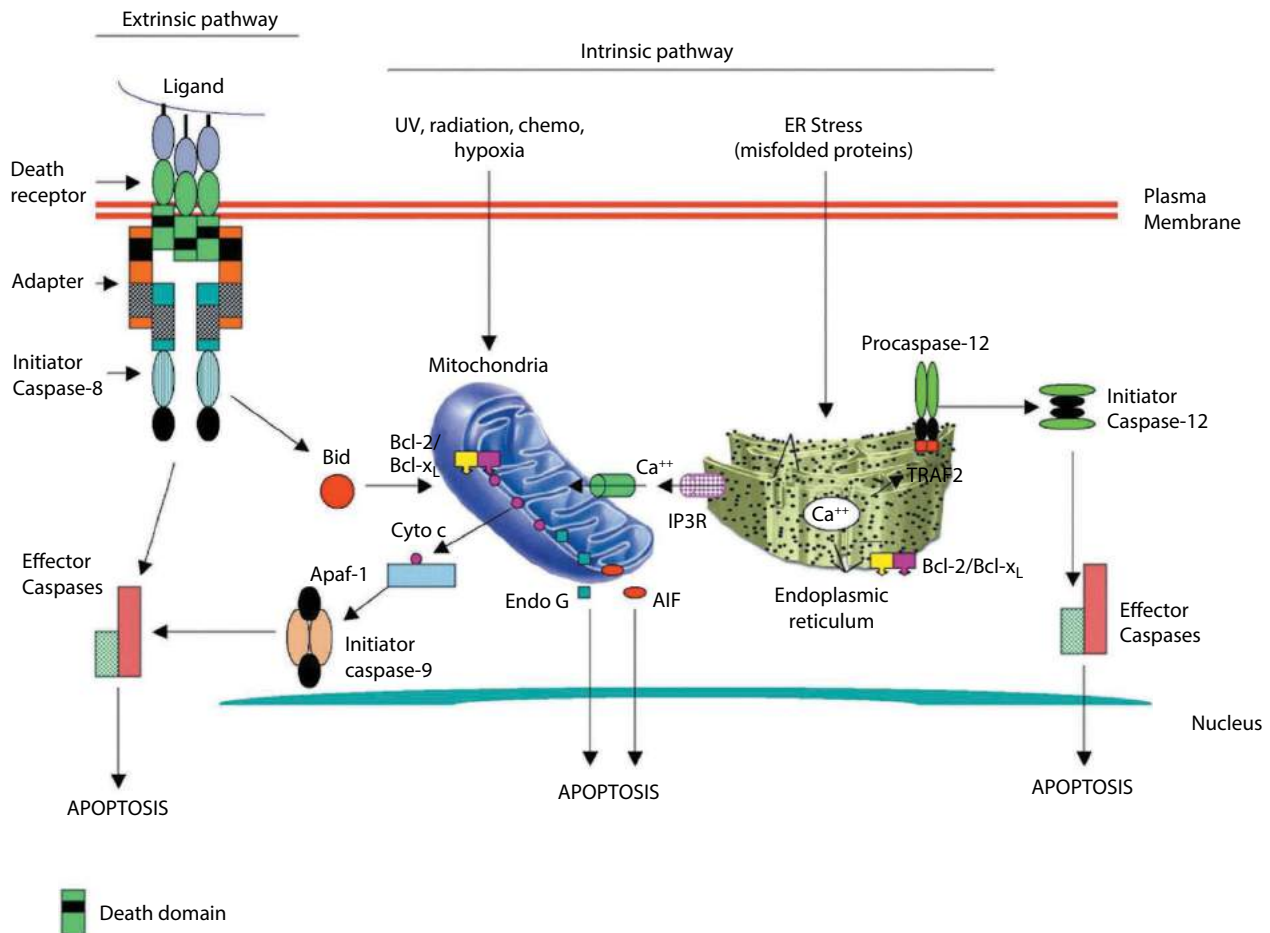


Figure 1.4 The two main pathways for the initiation of apoptosis: the extrinsic pathway and the intrinsic pathway. (Reproduced with open access from Gupta, S. et al., *Immun Ageing* 2006;3 (5), doi:10.1186/1742-4933-3-5.)

(DD), which is required for apoptotic signal transduction.²⁵ The DR TNF ligand (TNF-L), Fas ligand (FasL), and TRAIL induce apoptosis by binding to their cell membrane receptors. Following ligand binding, a conformational change in the intracellular domains of the receptors reveals the presence of a “death domain,” which allows the recruitment of various apoptotic proteins to the receptor. This protein complex is known as the death-inducing signaling complex (DISC). The final step in this process is the recruitment of one of the caspases, typically caspase-8, to the DISC. This leads to caspase-8 activation and apoptosis initiation.

Interestingly, there are also decoy receptors (DcRs) that compete to bind ligands to DRs, allowing the cell to escape death ligand-induced killing. DcR1 and DcR2 compete with DR4 or DR5 to bind to TRAIL. DcR3 competes with Fas to bind to the FasL.

The intrinsic cell death pathway involves the mitochondria and ER. The mitochondria-mediated pathway is induced by lethal intracellular signals such as oncogenic transformation and DNA damage. Mitochondria contain many proapoptotic proteins such as apoptosis-inducing factor (AIF), cytochrome *c*, and Smac/DIABLO. The last is a protein that directly neutralizes inhibitors of apoptotic proteins (IAPs), such as survivin,

originally described as an inhibitor of apoptosis proteins with a cell-cycle-specific function.²⁶ AIF, cytochrome *c*, and Smac/DIABLO are released from the mitochondria following the formation of a pore in the mitochondrial membrane called the permeability transition (PT) pore. These pores are thought to form through the action of the proapoptotic members of the bcl-2 family of proteins, which in turn are activated by apoptotic signals such as cell stress, free radical damage, or growth factor deprivation.²⁷ In particular, AIF and Smac/DIABLO were also reported to be involved in the mitochondrial death pathway related not to apoptosis but to the apoptosis-like death pathway.²⁸ The release of cytochrome *c* from the mitochondria is a particularly important event in the induction of apoptosis. When cytochrome *c* has been released into the cytosol it interacts with a protein called Apaf-1. This interaction leads to the recruitment of procaspase-9 into a multiprotein complex with cytochrome *c* and Apaf-1 called the apoptosome. This process and the apoptosis induction require adenosinetriphosphate (ATP); however, if ATP levels are insufficient to complete the apoptotic process, the mode of death may be directed toward necrosis.

The bcl-2 proteins are a family of proteins involved in the response to apoptosis. Some of these proteins (such as bcl-2

and bcl-X_L) are antiapoptotic, whereas others (such as Bad, Bax, or Bid) are proapoptotic. The sensitivity of cells to apoptotic stimuli can depend on the balance of pro- and antiapoptotic bcl-2 proteins. When there is an excess of proapoptotic proteins, the cells are more sensitive to apoptosis, but when there is an excess of antiapoptotic proteins, the cells will tend to be more resistant. An excess of proapoptotic bcl-2 proteins at the surface of the mitochondria is thought to be important in the formation of the PT pore.²⁷ The proapoptotic bcl-2 proteins are often found in the cytosol, where they act as sensors of cellular damage or stress. Following cellular stress, they relocate to the surface of the mitochondria, where the antiapoptotic proteins are located. This interaction between proapoptotic and antiapoptotic proteins disrupts the normal function of the antiapoptotic bcl-2 proteins and can lead to the formation of pores in the mitochondria and the release of cytochrome *c* and other proapoptotic molecules from the intermembrane space. This in turn leads to the formation of the apoptosome and the activation of the caspase cascade. The *bcl-2* gene has been shown to be transcriptionally repressed by *p53*. The *p53* tumor suppressor gene codes for the p53 protein and plays an important role in the control of the cell cycle, apoptosis, senescence, differentiation, and accelerated DNA repair.²⁹ DNA damage caused by exposure to ionizing radiation, UV light, or some exogenous or endogenous chemical mutagens, which results in DNA strand breakage, can trigger an accumulation of *p53*. This gene can activate transcription of growth regulatory genes such as *p21 WAF1/Cip1*, *GADD-45*, and *cyclin G*, resulting in G1 growth arrest, presumably to allow for repair of damaged DNA. If irreparable DNA damage exists, the cell becomes committed to the apoptosis pathway and is deleted by the system. For this reason, p53 is known as the “guardian of the genome.” Mutant p53 proteins may allow an escape from this surveillance mechanism and a generation of a malignant phenotype.

The ER is another important sensor of cellular stress that can withhold protein synthesis and metabolism to restore cellular homeostasis. Misfolded proteins are constantly produced; these proteins trigger a protective stress response, known as the unfolded protein response. Although this response may put off a cellular catastrophe for a short time, if the damage to the ER is too extensive, the damage can initiate PCD via the unfolded protein response or via release of calcium into the cytoplasm.³⁰ Thus caspase-12 is activated, which then engages caspase-9 and leads to the effector cascade recruitment.³¹ In addition, an intracellular calcium influx caused by ER stress induces the activation of a family of cytosolic proteases, the calpains (calcium-activated neutral proteases), which normally reside in the cytosol as inactive zymogenes.^{32,33} Calpains, kept in control by their natural inhibitor calpastatin, have been shown to act downstream of caspase. In fact, it has been demonstrated that vitamin D compounds trigger cell death in MCF-7 cells via calpains and independent of caspase activation, thus indicating a role of ER in certain types of caspase-independent cell death.³⁴ Disorders, such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and prion protein disease, all share the common features of accumulation and aggregation of misfolded proteins.³⁵

OTHER FORMS OF PCD

The exact phenotype of a dying cell is certainly dependent on many different factors that include the cell type, the cellular context, and the specific death stimulus.²⁸ Characteristic changes that differ in the various forms also include modifications of the cell shape and architecture, such as alterations of the cytoskeleton (Table 1.1). Any questions about the other forms of cell death remain unanswered: How important is the activation of the different PCD for the organism, and are all the mediators that trigger one type of death or another known? To these and other questions we will try to give an answer.

Table 1.1 Different Characteristics of the Cell Death Pathways

Types, characteristics	Apoptosis	Autophagic cell death	Paraptosis	Programmed necrosis	Necrosis
Triggers	Death receptors, trophic factor withdrawal, DNA damage, viral infections, etc.	Serum amino acid starvation, protein aggregates	Trophotoxicity	Ischemia, excitotoxicity	Excessive damage by physical or chemical injury, high intensities of pathological insult
Plasma membrane	Membrane-bound apoptotic bodies, blebbing	Elongation and invagination, blebbing	Shrinkage	Rapid loss of plasma membrane integrity	Rapid disintegration
Nucleus	Chromatin condensation, internucleosomal DNA cleavage (ladder)	Pyknosis in some cases, but neither prevalent nor striking, no DNA laddering	Late disintegration	No chromatin condensation, in some cases chromatin clustering to loosen speckles	Karyolysis
Cytoplasm	Condensation and shrinkage, cytoskeleton collapse	Vacuolization, autophagosome and autolysosome formation	Vacuolization	Swelling, extensive vacuolization	Condensation, loss of structure, fragmentation, swelling
Organelles	Preservation	Enwrapped by membrane sac. Autodigestion	Swelling	Swelling	Condensation and final disintegration

ACD

ACD is a long-known nonapoptotic cell death modality, also called type II cell death (to distinguish it from apoptosis or type I cell death).³⁶ Phagocytosis and autophagy are two well-known processes involved, respectively, in the removal of extracellular organisms and the destruction of organisms in the cytosol. Autophagy, for either metabolic regulation or defense, involves the formation of a double membrane called the autophagosome, which then fuses with lysosomes to degrade the contents, a process that has similarities to phagosome maturation. Autophagy is, in fact, normally activated during starvation by nutrient sensors to allow the recycling of substrates and organelles and to ensure the metabolic precursor.³⁷ Autophagy is also a means to eliminate dysfunctional organelles and allow a turnover of long-living proteins, thus preventing their pathological accumulation in the cells. Consequently, the cell “cannibalizes itself” from the inside (autophagy = “self-eating” in Greek). When this self-eating reaches excessive levels it may progress toward ACD, occurring in response to prolonged deprivation or stress, during embryogenesis, in adult tissue remodeling, in human diseases, or during cytotoxic drug treatment.³⁶ Autophagy is often observed when massive cell elimination is needed or when phagocytes do not have easy access to the dying cells. ACD is differentiated from apoptosis by certain peculiarities, including autophagosome and/or autolysosome formation, a vast autodigestion of organelles, a preserved nucleus until late stages (with the absence of DNA laddering), and cytoskeleton preservation until the final stages. In contrast to apoptosis, ACD occurs in a caspase-independent pathway. Interestingly, autophagy can be a factor in both the promotion and prevention of cancer, and its role may be altered during tumor progression.³⁸ The first autophagy gene identified in humans was *Beclin 1*. The heterogeneous disruption of this gene leads to increased tumorigenesis in mice.³⁹ *Beclin 1* is inhibited by its interaction with *Bcl-2*, which thus functions not only as an apoptotic suppressor, but also as an antiautophagic factor.⁴⁰ Some malignant cell types respond to anticancer agents by triggering autophagy, indicating the potential utility of ACD induction in cancer therapy. Cancer cells may need autophagy to survive nutrient-limiting and low-oxygen conditions, and autophagy may protect cancer cells against ionizing radiation by removing damaged elements. Autophagy and apoptosis can be observed simultaneously in the same tissue, and, in some cases, autophagy may precede and later trigger apoptosis when the autophagic capacity is overwhelmed.³⁶ In other settings, autophagy has been observed to delay or antagonize apoptosis, and there are also examples in which the two processes can be mutually exclusive.³⁶

For a deeper knowledge of this topic and for a better comprehension of the molecular pathways involved refer to the reference⁴¹.

PARAPTOSIS

A novel nonapoptotic PCD process designated paraptosis was described by Sperandio and colleagues.¹⁰

The features of paraptosis differ from those of apoptosis and involve cytoplasmic vacuolation, mitochondrial swelling, the absence of caspase activation, and typical nuclear changes including pyknosis and DNA fragmentation.¹⁰ There is increasing evidence that this alternative, nonapoptotic PCD exists in parallel with apoptosis. The neuropeptide substance P and its

receptor, neurokinin-1, mediate a nonapoptotic form of PCD resembling paraptosis in some cases.⁴² Activated microglia trigger neuronal cell death with ultrastructural characteristics of marked vacuolation and slightly condensed chromatin following the blockage of the caspase cascade.⁴³ In addition, ceramide induces nonapoptotic PCD with necrosis-like morphology in human glioma cells in the presence of pan-caspase inhibitors or during overexpression of *bcl-X_L*.⁴⁴ These examples support the theory that cells have other intrinsic programs for death that are distinct from apoptosis. This death program can be mediated by mitogen-activated protein kinases and can be triggered by the TNF-R family member *TAJ/TROY*, capable of inducing apoptosis independent of DNA fragmentation and caspase activation, and the insulin-like growth factor I receptor.^{1,45} The idea that PCD might be induced by hyperactivation of a trophic factor receptor (trophotoxicity) is compatible with an earlier observation that some trophic factors may increase neuronal cell death, for example, that induced by excitotoxicity.⁴⁶ Such an effect might be protective against neoplasia in that it may eliminate cells that would otherwise undergo autocrine loop-stimulated oncogenesis. The resulting program would necessarily be nonapoptotic, because trophic factors inactivate apoptotic signaling.

NECROSIS AND PROGRAMMED NECROSIS

For a long time necrosis was considered as an alternative to apoptosis^{7,8}; however, necrosis, once thought of as simply a passive, unorganized way to die, in the recent past, has emerged as an alternative form of PCD, the activation of which might have important biological consequences, including the induction of an inflammatory response.⁴⁷ The term “necrosis” has, therefore, been wrongly used for years to define an alternative mode of cell death. It is now evident that we cannot refer to necrosis to mean a particular program of death and that this term should be used to describe what happens after a cell is dead. It is, therefore, more correct to use the term “programmed necrosis,” “necrosis-like PCD,” or “necroptosis” when we describe certain kinds of cell death governed by a specific genetic program and quite different from classical apoptosis or not falling within the cell death pathways described earlier in this chapter.⁶ There are many examples of programmed necrosis being a normal physiological and regulated (programmed) event. Signaling pathways (e.g., DRs, kinase cascades, and mitochondria) participate in both processes, and, by modulating these pathways, it is possible to switch between apoptosis and programmed necrosis; moreover, antiapoptotic mechanisms (e.g., *bcl-2*/*bcl-x* proteins, heat shock proteins) are equally effective in protecting against apoptosis and programmed necrosis.

There are several examples of necrosis during embryogenesis, normal tissue renewal, and the immune response.⁷ The core events of programmed necrosis are bioenergetic failure and rapid loss of plasma membrane integrity. The consequence is the release of cellular contents, a number of which serve as damage-associated molecular patterns (DAMPs), which can potentiate inflammation.⁴⁸ These events can result from specific molecular events that occur in the dying cell, including increased mitochondrial reactive oxygen species production, channel-mediated calcium uptake, activation of nonapoptotic proteases, and/or enzymatic destruction of cofactors required for ATP production. Karyolysis of the nucleus occurs as a consequence of the complete dissolution of the chromatin due to

the activity of specific DNase. In addition, these necrotic mediators are often induced in the dying cell simultaneously and enhance each other's ability to initiate the demise of the cell.⁴⁹ Calpain and lysosomal cathepsin activation have been shown to contribute to necrotic cell death.

To complicate the intricate net of terminologies used to define the area of apoptosis versus necrosis, the term "oncosis" (from the Greek word for swelling), a form of cell death activated by ischemia, has also been used through the years to define all the situations in which marked cellular swelling occurred. Oncosis may result from toxic agents that interfere with ATP generation or processes that cause uncontrolled cellular energy consumption. One potential mediator of oncosis is a calpain-family protease (possibly a mitochondrial calpain), which suggests that oncosis may turn out to be related to, or synonymous with, a calcium-activated programmed necrosis cell death. This term may designate any programmed cellular suicide characterized by marked swelling, whereas the term "necrosis" refers to the features that appear after the cell has died.⁶ Necrosis may be either oncotic or apoptotic in origin. In this context, oncosis comprises the prelethal changes leading to ischemic or coagulation necrosis, whereas necrosis describes a morphology but not a process, thus underscoring the final feature of a dead cell.

Pyroptotic Death

Pyroptosis is a form of cell death that depends on the activation of caspase 1.⁵⁰ Pyroptosis can be distinguished from apoptosis in some aspects by the absence of cytochrome c release, membrane blebbing and for the induction of an inflammatory process with cytokines release. Cells dying by pyroptosis exhibit cytoplasmic swelling and rupture of the plasma membrane, features that are common to necrosis. Conversely, both pathways involve DNA cleavage.

Caspases involved in the induction of pyroptosis are caspase-1, but also caspase-11 has found to be involved. Caspase 1 is synthesized as an inactive zymogen and only after controlled dimerization in inflammasomes is activated triggering the secretion of potent pro-inflammatory cytokines and pyroptosis. Inflammasomes are a group of protein complexes that recognize a diverse set of inflammation-inducing stimuli that include PAMPs (pathogen-associated molecular patterns) and DAMPs. On receiving an activating signal inflammasomes sensors recruit pro-caspase-1, the zymogen is converted into enzymatically active protease, which in turn cleaves pro-interleukin-1 β (IL-1 β) and pro-IL-18 to produce the active cytokines.

Inflammasome-mediated processes are important during microbial infections and also in regulating both metabolic processes and mucosal immune responses.⁵¹ It has been shown that the inflammasomes component can be expressed in various cell types involved in wound healing including macrophages and keratinocytes, playing an important role in early inflammatory response in tissue repair.⁵² Finally, findings support a crucial role for IL-1 β and inflammasome components in a variety of allergy-related disorders.⁵³

APOPTOSIS AND HUMAN DISEASES

Nonregulated apoptosis involves different pathophysiologic situations, such as malignant and premalignant conditions, neurologic disorders (e.g., Alzheimer's disease, prion-associated

disorders), cardiac disease (ischemic cardiac damage, chemotherapy-induced myocardial suppression), immune system disorders (e.g., acquired immune deficiency syndrome [AIDS], type I diabetes, systemic lupus erythematosus [SLE], Sjögren syndrome), intestinal disorders, and kidney disease.² In particular, diseases characterized by the accumulation of cells include cancer, autoimmune diseases, and certain viral illnesses. Cell accumulation can result from either increased proliferation or the failure of cells to undergo apoptosis in response to appropriate stimuli.

Cell Death in Cancer

Tumor growth occurs when the cellular birth rate exceeds the death rate. Control of cell growth is important in the process of normal development and tissue homeostasis, and in pathologic conditions, such as neoplasia. Growth arrest and cell death are also important in normal and neoplastic growth.

Inactivation of apoptosis is a hallmark of cancer, an obligate ritual in the malignant transformation of normal cells. By inactivating apoptosis, cancer cells enhance their chances of survival and increase their resistance to chemotherapeutic agents. Because apoptosis is a gene-controlled process, it is susceptible to genetic manipulation for therapeutic purposes, such as in cancer treatment. The acquisition of resistance to apoptosis is important in the transition from normal melanocyte to melanoma. Apoptosis is, in fact, critical for epidermal homeostasis, representing a key protective mechanism removing premalignant cells that have acquired mutations.⁵⁴

Melanoma is the most aggressive form of skin cancer, notoriously resistant to current modalities of cancer therapy and known to be a tumor with an elevated metastatic ability.⁵⁵ Although melanoma is currently more often diagnosed in an early stage of disease and therefore shows a better overall survival, when tumor cells are detected in the regional lymph node, the patient has a poorer prognosis.

One of the earliest events in melanoma progression involves the unregulated proliferation of melanocytes. In this stage of melanoma progression, the cells lose their ability to maintain the cell-cycle controls that function in normal unstimulated melanocytes. This loss of cell-cycle control can lead to sustained proliferation, decreased apoptosis, or both. It also has been reported that melanocytes displayed a broad expression of apoptotic inhibitors to maintain their longevity, at the cost of the nonelimination of damaged cells, thus resulting in a high probability of developing melanoma.⁵⁶ In contrast, keratinocytes are more prone to undergoing apoptosis to ensure a rapid turnover and efficiently remove damaged cells and meet their functional needs in the skin.

Melanoma cells are resistant to a wide range of antineoplastic treatments due to their ability to evade the cytotoxic action of different insults, such as DNA damage, microtubule destabilization, or topoisomerase inhibition,⁵⁵ showing, in contrast, strong resilience. Melanoma cells *in vivo* demonstrate low levels of spontaneous apoptosis compared with other tumor cell types, and resistance to apoptosis is associated with increased resistance to chemotherapeutic agents.⁵⁶ The knowledge acquired about the altered apoptotic mechanism in melanoma has focused the attention of researchers on molecules able to compensate for or bypass the cell death defects and on the development of new chemotherapeutic strategies that facilitate the death of cancer cells.

Cell Death and Autoimmune Disorders

Physiologic regulation of cell death is essential for the removal of potentially autoreactive lymphocytes during development and for the removal of excess cells after the completion of an immune response. Failure to remove autoimmune cells that arise during development or that develop as a result of somatic mutation during an immune response can result in autoimmune disease.⁵⁷ Upregulated levels of soluble Fas, which might competitively inhibit FasL–Fas interactions, have been documented in many autoimmune disorders, such as rheumatoid arthritis, SLE, and pemphigus vulgaris (PV).⁵⁸ PV is a chronic autoimmune cutaneous disease characterized by circulating autoantibodies that cause blisters and erosions on the skin and mucous membranes.⁵⁹

Circulating autoantibodies bind with the epidermal cell membrane and cause cell–cell detachment (acantholysis), leading to epidermal tissue damage. In recent years, the idea that apoptosis might play a central role in the induction of acantholysis has gained momentum. In support of this supposition, one study has demonstrated the proteolytic cleavage of desmoglein 3 (PV antigen) by caspase-3 during apoptosis; thereby causing desmosome disruption only after the induction of apoptosis.⁶⁰

We have shown the ability of pemphigus serum and captopril to induce apoptosis in human keratinocytes.⁶¹ In particular, we have demonstrated that a drug (captopril) or antibodies (PV serum) acting, respectively, by a biochemical or immunologic mechanism induced acantholysis through the same genetic program leading to PCD.

Another group has demonstrated the therapeutic action of intravenous immunoglobulin (IVIg) in PV.⁶² In the plethora of biologic effects exerted by IVIg administration (acceleration of the clearance of autoantibodies, modulation of serum levels of proinflammatory cytokines, induction of immunocompetent cell death), an array of antiapoptotic effects should also be mentioned. IVIg inactivates FasL, protects target cells from apoptosis by upregulating Bcl-2 expression, interferes with TNF- α and interferon- γ signaling pathways, and increases sensitivity to corticosteroid action, thus strengthening the idea that apoptosis may play an important role in the onset of the disease.

CONCLUSIONS

Even in diseases in which the affected cells have been shown to die with “apoptotic morphology,” one cannot exclude the possibility that a caspase-independent cell death program occurs in concert with a caspase-dependent program.⁶³ The knowledge of the genetic program underlying the onset of the disease might help the researcher to use the appropriate genetic therapy by inhibiting one pathway or another. In such cases, it is important to understand whether a program of death is controlled by caspase activation. The inhibition of the caspase cascade to control apoptosis induction in some degenerative diseases can delay (but not prevent) the progression of the disease if some other caspase-independent program of death is operating.

The occurrence of one or another of the different programs of cell death is an important aspect to take into account. In fact, one of the cancer therapy approaches is to kill cancer cells by apoptosis. It is also known that cancer cells are selected for their acquired resistance to apoptosis and, therefore, it is important to be able to exploit other genetic programs to complement or integrate apoptosis and perhaps open new frontiers for tumor therapy.

Despite the numerous models proposed to categorize PCD, it is difficult to give one single definition, and probably also incorrect, due to the overlap and shared signaling pathways of the different death programs. It has, therefore, been postulated that the dominant cell death phenotype, triggered by cytotoxic agents, is determined by the most readily available death program.⁶⁴

Besides caspases, a broad spectrum of proteases can carry out PCD, with the participation of different cellular organelles, including mitochondria, lysosomes, or ER, which can act independently or actively collaborate with each other. The multicellular organism can take advantage of the existence of multiple death pathways, because they offer protection, for example, against the development of malignant diseases.

Many difficulties and obstacles have to be overcome before a cell becomes a tumor cell, and this in part explains the rarity of cancer, considering the number of cell divisions and mutations that occur during human life. The control of PCD may ultimately offer a new perspective not only in cancer immunotherapy but also in the treatment of autoimmune diseases and neurodegenerative disorders.

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Clean and aseptic technique at the bedside

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Cutaneous surgical interventions are becoming more and more popular as this area of dermatology continues to rapidly expand. Dermatologists are performing progressively more surgical procedures in their private offices.¹ A survey performed by the American Society for Dermatologic Surgery (ASDS) in 2014 showed that 9.5 million treatments were performed, up 22% from the year prior.² These outpatient procedures allow the dermatologist to provide more comprehensive care to the patient and present the patient with a more affordable option, because outpatient procedures under local anesthesia are less expensive than procedures completed in the hospital setting.^{1,3}

With the upsurge in the number of cutaneous surgeries, an important goal remains to keep patients free of nosocomial and surgical site infections (SSIs). Traditionally, dermatologic procedures and surgeries have benefited from relatively low infection rates,^{4,5} despite varying infection-control practices.¹ Strict adherence to aseptic technique is required to maintain this low rate of infectious complications. In addition to the principles of asepsis, the surgeon must also minimize patient and environmental risk factors, achieve adequate preoperative preparation, decide if antibiotic prophylaxis is necessary, as well as maintain proper surgical suite protocol and surgical technique.

SURGICAL SITE INFECTIONS

Postoperative infections after dermatologic procedures are rare. These surgeries are largely considered either “clean” or “clean-contaminated,” with infection rates of less than 5%⁶ and 5%–10%, respectively.⁴ Studies examining the rate of infectious complications following dermatologic procedures have indicated an even lower incidence in this field. Two studies reported infectious complication rates of 2% following outpatient dermatologic procedures,^{6,7} and another study describing the complications following Mohs Micrographic Surgery showed an infection rate of 0.43%.⁸

Complication rates have been shown to be higher in dermatology inpatients. A recent study examining the complication rate of diagnostic skin biopsies performed on inpatients found that 29% of patients developed postoperative complications, with 93% of these complications being wound infections.⁹ This increased rate may be attributable to differences in the patient population. Dermatology inpatients are more likely to be widely colonized with *Staphylococcus aureus*, to have extensive skin disease, and/or to be systemically unwell.^{9,10}

Clinically, SSIs are recognized by the extrusion of pus from a wound that may also exhibit some of the cardinal signs of inflammation in the surrounding skin: redness, heat or warmth, swelling, and pain. Patients may also display systemic signs of infection, such as fever or chills. Laboratory

confirmation is also necessary to make the diagnosis. Bacterial cultures taken from the site should demonstrate a concentration of at least 100,000 colony-forming units per square centimeter. Treatment of infected wounds requires effectively reducing the bacterial concentration, and debridement is the most important method of achieving this. Other techniques include the use of topical antibacterials, frequent dressing changes, and biologic dressings.

The most common cause of wound infections is the patient’s endogenous skin flora,^{11,12} with the absolute most common pathogen being *S. aureus*.^{11,13} Recent research indicates that nasal *S. aureus* carriage is an important risk factor for SSI.^{14–17} These microorganisms tend to colonize the uppermost layers of the skin and hair follicles; approximately 10%–20% of bacteria penetrate deeper into the hair follicles, however, where they can escape routine disinfection methods. Despite sterilization and disinfection procedures, the skin remains contaminated, because these elusive organisms are a viable source of recolonization after the removal of superficial bacteria.¹⁸

Researchers have suggested that the rate of SSIs might be decreased further by decreasing the number of skin flora.¹¹

PATIENT RISK FACTORS

Many factors contribute to the likelihood of a patient contracting a surgical wound infection. Patient-specific characteristics often cannot be eliminated or modified and must be dealt with on an individual basis. The most common patient-specific risk factors encountered are specific medical conditions that decrease the immune status of the individual.^{19–21} Diabetes mellitus, for example, has been shown to increase the risk of infection and to have a negative effect on wound healing. Smoking also has been shown to have similar harmful effects, perhaps from the nicotine induced vasoconstriction, reducing blood flow to the skin. In a study examining risk factors for SSIs, diabetes, obesity, and smoking all were found to be independent risk factors. Patients should be encouraged to abstain from smoking in the perioperative period as this will decrease the risk of SSI and tissue necrosis.^{13,22,23} Other risk factors include an immunocompromised state secondary to a variety of causes (e.g., human immunodeficiency virus/acquired immune deficiency syndrome [HIV/AIDS], corticosteroids, malignancy, advanced age) and concomitant infections, such as urinary tract infections, which must be treated before the surgical procedure is performed. Additionally, patients with a history of infective endocarditis and recent joint replacement are considered high risk.^{24–26} Patients with concurrent infections have a markedly increased risk for developing SSIs, even if the infection is distantly located from the wound.^{19–21} Location of surgery also contributes to the risk of SSI development. Due to vascular factors, the lower

extremities pose the highest risk^{22,27}; whereas the well-vascularized face presents the lowest risk of infection.²²

ENVIRONMENTAL RISK FACTORS

Factors extrinsic to the patient also contribute to the development of SSIs. These environmental risk factors can often be modified and/or eliminated to decrease the patient's risk of acquiring infection.

DECONTAMINATION OF SURGICAL EQUIPMENT

Surgical procedures involve the use of instruments that may come into contact with patient skin, mucous membranes, and/or sterile body cavities. Viable microorganisms and spores must be removed from reusable surgical equipment after each use to decrease the risk of infection and prevent cross-contamination between patients. Microbial decontamination may be achieved by cleaning, disinfection, and/or sterilization.^{28–30}

Cleaning

Cleaning removes viable microorganisms and the organic matter in which they survive from the surfaces of medical equipment. Although cleaning does not kill these bacteria, spores, or viruses, it remains an essential part of the decontamination process as the removal of these surface organisms facilitates disinfection and sterilization of equipment. Organic matter may interfere with adequate decontamination by inactivating disinfectants and sterilants and preventing direct contact with microbial cells. Cleaning is most effective when performed as soon as possible after equipment use. Cleaning should only be performed as the sole method of decontamination on non-critical items—that is, items that come into contact only with normal and intact patient skin. In general, automated cleaning methods, such as washer disinfectors and ultrasonic cleaners, are superior and preferable to manual methods (paper towels, wet wipes, etc.) as these methods produce standardized results.^{28–31}

Disinfection

Disinfection refers to the chemical destruction of the majority of the viable microorganisms residing on a given surface. Although some spores may also be targeted, disinfection alone does not reliably kill or inactivate all spores and viruses. In situations where sterilization by steam under pressure (autoclaving) is inappropriate or could damage medical equipment, the disinfection process may be utilized to decontaminate semi critical and critical items that have been exposed to nonintact patient skin, mucous membranes, or sterile body cavities. Disinfectants may be compromised by some organic matter, highlighting the importance of proper cleaning prior to disinfection. Disinfection may be achieved by either chemical or physical processes, with the latter being preferred as they are more amenable to monitoring and standardization.^{28–31}

Sterilization

Sterilization refers to the complete destruction or elimination of all transmissible organisms from a surface, including bacteria, spores, viruses, and fungi. Given its thoroughness, this process is appropriate for critical equipment and instruments. Many different types of sterilization exist; the most commonly used

methods for surgical equipment include autoclaving, dry heat, ethylene oxide, and irradiation.^{28,29,31}

PREOPERATIVE SKIN ANTISEPSIS

Alcohol

Alcohol is one of the oldest and most effective antiseptics available. It is abundant, rapid acting, and inexpensive. It is appropriate for use in minor, clean procedures, and has germicidal properties against most bacteria, fungi, and viruses. Some bacterial spores may show resistance. Its use is often limited, however, by its flammability and potential for skin irritation.^{20,21}

Iodinated Preparations

Betadine and other iodophors have broad-spectrum antimicrobial activity. These compounds are rapid acting and are bactericidal within minutes; however, iodinated compounds are effective only when dry, and they lose their bactericidal effect when removed from the skin. They also leave a yellowish discoloration on the skin, are irritating, and are inactivated by contact with blood and other serum proteins. Although iodophors are relatively safe, when used chronically in pregnant women, associated hypothyroidism has been reported in neonates.^{20,21,32}

Chlorhexidine

Chlorhexidine gluconate (CHG) is active against a wide range of gram-positive and negative bacteria, viruses, and yeast. It is rapid acting, does not stain the skin, and is not inactivated by contact with blood or other serum proteins. An additional benefit of CHG is that it demonstrates prolonged antimicrobial activity by binding to the stratum corneum of the skin, allowing for efficacy even after removal. In comparison with the iodophors, CHG has been shown to lead to a greater reduction in bacterial counts and demonstrates a cumulative effect after repeated exposure.^{33–38} Cases of keratitis and ototoxicity have been reported after prolonged, direct contact with patients' eyes and tympanic membranes. The majority of these instances occurred in patients exposed to CHG while under general anesthesia, who were unable to respond to the antiseptic-induced irritation.^{20,21,39–41}

Preparation of the Skin

Before prepping the skin with antiseptic, all visible dirt and organic matter should first be removed. Antiseptic should then be applied to the area where the skin incision will be made, extending outward in concentric circles. A large enough area should be prepped so that the incision can be extended or new incisions/drain sites can be made if necessary.^{20,21}

Hair Removal

Hair that may contaminate the operative site should be removed with scissors or by clipping prior to the procedure. Shaving of the area should not be performed within 24 hours of the surgical procedure as open skin, cuts, and scratches increase the risk of infection. If shaving is necessary to remove the hair, the skin should first be scrubbed with an antiseptic and then shaved immediately prior to the procedure. Adhesive tape can then be used to remove excess pieces of hair.^{20,21}

Hand Washing

The majority of hospital-acquired infections are thought to be transmitted via the hands of health care workers. As many as 10,000 colony-forming units can be transmitted by brief hand contact alone.⁴² Studies have found hand washing to be the most effective method of reducing hospital-acquired infections.⁴³ These results assume satisfactory hand-washing methods are undertaken; past studies have shown that adequate washing is hardly achieved and that approximately 89% of staff do not cleanse the entire hand surface.^{19,44} Hands should be washed before and after each patient contact.⁴⁵ Three varieties of hand-washing agents are currently available.

Plain Soaps

Plain soaps derive their cleaning activity from their detergent bases. Soap and water are most effective in removing dirt, soil, and some organic substances. Although soaps have no inherent antimicrobial activity and cannot remove resident microorganisms, they can eliminate transient microorganisms from the hands^{28,45,46}; however, hand washing with soap can also cause an increase in the total number of bacteria on the hands.^{19,47} This paradoxical increase has been explained by enhanced release of bacterial particles from the skin after hand washing. Soaps may also contaminate the hands if the source has become extrinsically contaminated. Several cases of extrinsic contamination of nonmedicated liquid soaps with *Serratia marcescens* have been previously documented.^{41,42}

Antiseptic Detergents

Antiseptic detergents, like plain soap and water, are also effective at removing dirt and soil. These agents do have antimicrobial activity and are more effective in removing both transient and resident microorganisms from the hands.^{19,28,47}

Alcohol-Based Hand Rubs

Alcohol-based hand rubs are the most effective at removing microorganisms from the hands and reducing hand flora. These solutions have germicidal activity against a broad range of gram-positive and -negative bacteria, including some multidrug resistant pathogens. Alcohols are also active against certain viruses when tested in vitro. To be most effective, these hand rubs should contain 60%–95% alcohol.²¹ Additionally, these agents are simple and quick to use and require less effort than traditional soaps, which may lead to increased compliance with hand washing. Alcoholic hand rubs should not be used on visibly soiled hands as these agents are not effective at removing dirt or other physical contaminants. In this case, hands should first be washed with soap and water before applying the alcohol-based hand rub.^{20,28,47}

Scrubbing

“Scrubbing” refers to the process by which members of the surgical team who will be in contact with the sterile field or instruments significantly decrease the bacterial counts on the hands and forearms. Although the majority of dermatologic surgeries are performed on an outpatient basis, some procedures require the dermatologist to perform the traditional surgical scrub.

Three types of antiseptics exist for scrubbing: aqueous scrubs, alcohol rubs, and alcohol rubs with additional active ingredients. Aqueous scrubs are water-based preparations with active ingredients such as CHG and povidone–iodine. Alcohol rubs, described earlier in this chapter, are also approved for the purpose of scrubbing. The third class of antiseptic is a

modification of the alcohol rub with the addition of active ingredients (usually CHG or povidone–iodine) to impart greater antimicrobial activity.²³ CHG and povidone–iodine are the recommended antiseptics for scrubbing in the United States.²¹

The quality and effectiveness of scrubbing is also affected by factors other than the choice of antiseptic. The condition of the skin on the hands, the scrubbing technique and duration, and the gowning and gloving technique must all be considered. Although studies have not yet shown an optimum duration of scrubbing, it has been shown that scrubbing for 2 minutes is as effective as for 10 minutes. The first scrub of the day should always be the most thorough, and it is at this time that surgical team members should thoroughly clean under their fingernails. The hands and forearms should then be vigorously cleaned with a brush up to the elbows and rinsed. Hands and arms should be held up with the elbows flexed, avoiding contamination, until dried with sterile towels immediately before dressing in a sterile gown and gloves.²¹

WOUND CLASSIFICATION

Antibiotic selection to prevent wound infection first requires a discussion of wound types. Clean wounds (class I) refer to surgical sites without contamination that do not involve entry into the gastrointestinal, respiratory, or urinary tracts. No inflammation is present at the wound. Risk of infection is less than 5%. Most dermatologic surgeries fall into this category. Clean-contaminated wounds (class II) involve controlled entry into the gastrointestinal, respiratory, or urinary tracts without spillage or gross contamination. The risk of infection of dermatologic surgery into a class II wound is approximately 10%. Contaminated wounds (class III) occur by various means: breaks in sterile technique, spillage of gastrointestinal or urinary tract contents, or traumatic accidents. This category also includes wounds with nonpurulent discharge. The infection rate from dermatologic surgery in a class III wound is 20%–30%. Finally, dirty wounds (class IV) include wounds with purulent discharge, fecal contamination, foreign bodies, or necrotic tissue or entry into a perforated viscus. Risk of infection is 40%.^{20,43}

ANTIMICROBIAL SELECTION

Whether to use antibiotic prophylaxis in dermatologic surgery is a frequent topic of debate. As discussed earlier in this chapter, most dermatologic procedures are performed on class I or class II wounds and carry an inherent risk of postoperative infection of no greater than 10%. Although it is clear that antibiotic prophylaxis can reduce this already low infection rate, antimicrobials themselves may cause problems. Use of antimicrobials can add to the number of adverse drug events and allergic reactions, promote drug-resistant organisms, and interact with concomitant medications, in addition to adding cost.^{20,44,48} Antimicrobial prophylaxis should not be used routinely for dermatologic procedures, but rather in a select group of patients at high risk for SSI or other infectious complications. Class I wounds do not require antimicrobial prophylaxis, nor do most cases of class II wounds. Antimicrobials may be beneficial for class II wounds in which oronasal or anogenital mucosae are breached or for large axillary or inguinal wounds.²⁰ In class III and IV wounds, antimicrobials serve a therapeutic rather than prophylactic purpose, and should be used routinely.

Besides reducing SSIs, another reason dermatologists often use antimicrobial prophylaxis is for the prevention of

infection at a distant site such as a heart valve or prosthetic joint.^{20,45} Endocarditis or seeding of a prosthetic joint theoretically can be caused by bacteremia induced during skin surgery. The incidence of bacteremia during skin surgery has been found to be only 0.7%,⁴⁶ which compares favorably to the 0%–2.1% incidence of bacteremia in random blood cultures of healthy volunteers.⁴⁷ The routine use of antimicrobial prophylaxis during dermatologic procedures in otherwise healthy individuals for prevention of endocarditis or joint infection seems unwarranted. In fact, no randomized clinical trial to date has established that antimicrobial prophylaxis prevents endocarditis.

Should the decision to use antimicrobials be made, the next most important step is to use them optimally. Effective prophylaxis provides a high blood and tissue level of antimicrobial at the time of anticipated bacteremia. Antimicrobials given at the conclusion of a procedure are not as effective in preventing infection, and after the wound is closed, there is generally no longer any risk of contamination. A large loading dose of the appropriate antimicrobial should be given approximately one hour before surgery.

The route of antimicrobial prophylaxis is generally thought of as either oral or intravenous. Intra-incisional antimicrobial prophylaxis injected along with buffered lidocaine and epinephrine has also shown to reduce wound infection. Benefits of intra-incisional antimicrobial prophylaxis include immediate delivery to the site where it is needed, ease of use (in the same syringe as anesthetic), enhanced compliance, and relatively low cost.^{25,41,49} Additionally, because the dose of intra-incisional antimicrobials is low compared with the amount necessary in oral or intravenous prophylaxis and is applied locally, the risk of systemic side effects and bacterial resistance is theoretically lower. Intra-incisional antimicrobials are not widely used currently, but their potential benefits warrant further investigation. In the future, they may become more common as an alternative to traditional prophylaxis.

For class III and IV wounds, in which antimicrobial use is recommended routinely, the choice of antimicrobials should be based on the presumed organism causing the infection. If a wound culture with sensitivities is available prior to a procedure, this should obviously be taken into account prior to antimicrobial selection. In the absence of wound culture results, first-generation cephalosporins are a good choice due to their excellent coverage of staphylococcal organisms (the most common cause of wound infection) as well as common gram-negatives such as *Escherichia coli* and some *Proteus* species.^{48,50} Penicillins, especially beta-lactamase-resistant variants are also good choices. Many patients have penicillin sensitivity, and due to cross-reactivity with cephalosporins, both of these first-line choices would be inappropriate for these patients. In these cases, macrolides (e.g., erythromycin) or quinolones (e.g., ciprofloxacin) can be used. Current American Heart Association guidelines recommend amoxicillin as the first choice for standard prophylaxis (or ampicillin for patients unable to take oral medications), with clindamycin as an alternative for patients with penicillin allergy.⁴⁹

CONCLUSIONS

With the number of dermatologic procedures being performed increasing each year, ensuring a minimal amount of nosocomial and SSIs is important, while understanding the inherent risk factors of a procedure and that using proper aseptic technique can help prevent such complications. Surgical equipment decontamination, preoperative skin asepsis, and proper hand

washing are all techniques that can keep infections to a minimum. Antimicrobial prophylaxis is generally unnecessary for dermatologic procedures, as the risk of adverse events due to the antimicrobials often outweighs the benefit of further reducing an already low incidence of infection.

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New antimicrobials

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With the continuing development of clinical drug resistance among bacteria and the advent of resistance to the released agents quinupristin-dalfopristin and linezolid, the need for new, effective agents to treat multidrug resistant gram-positive infections remains important. With treatment options limited, it has become critical to identify antimicrobials with novel mechanisms of activity. Several new drugs have emerged as possible therapeutic alternatives. This chapter focuses on agents recently introduced to the clinic and those presently in clinical development for the treatment of skin and skin structure infections (SSSIs). In addition, novel antifungal agents will be reviewed, as will novel dosing of antiviral agents for herpes labialis.

NOVEL ANTIMICROBIAL AGENTS (TABLE 3.1)

There has been an alarming increase in the incidence of gram-positive infections, including resistant bacteria such as methicillin-resistant *Staphylococcus aureus* and drug-resistant pneumococci. Vancomycin has been considered the drug of last defense against gram-positive multidrug-resistant bacteria, but strains of vancomycin-resistant bacteria, including vancomycin-resistant enterococci (VRE), began to emerge by the late 1980s. Strains of vancomycin-intermediate resistant *Staphylococcus aureus* (VISA) are now being isolated.¹

Gram-positive bacteria, such as *S. aureus* and *Streptococcus pyogenes*, are often the cause of both uncomplicated and complicated skin and skin structure infections. Uncomplicated infections are mild, localized to the skin, and responsive to topical or systemic antibiotics. This category includes simple abscesses, impetiginized lesions, furuncles, and cellulitis. Complicated infections are those involving deeper soft tissues, requiring surgical intervention or associated with significant systemic disease or comorbidities. Corresponding clinical entities include surgical wound infections, infected ulcers or burns, severe carbuncles, erysipelas, and necrotizing fasciitis.

Several novel agents have emerged as possible therapeutic alternatives. These include linezolid, quinupristin/dalfopristin, daptomycin, oritavancin and dalbavancin, the quinolones, moxifloxacin and gatifloxacin, and tigecycline.

Linezolid

Linezolid is an oxazolidinone antibiotic, shown to be effective for nosocomial and community-acquired pneumonias, vancomycin-resistant *Enterococcus faecium* (VREF) infections, and skin infections due to certain staphylococcus or streptococcus species.² The oxazolidinones are a novel class of antimicrobials first discovered in 1987.³ They are the first new antimicrobials to have been discovered in the past 35 years.

Mode of Action

Cellular Mechanism

Oxazolidinones, and specifically linezolid, are theorized to act by inhibiting the initiation phase of translation and thus interfering with bacterial protein synthesis.⁴ Linezolid binds to the 23S portion of the 50S ribosomal subunit, specifically to the A site of the protein translation complex, where it prevents initiation of complex formation. It was originally thought that this early inhibition of protein synthesis was a unique mechanism that limited cross-resistance with other antimicrobial agents, since no preexisting resistance mechanism existed.⁴ Unfortunately, recent studies have shown that several types of modifications at the linezolid binding site do cause resistance.

Pharmacokinetics

Oral bioavailability of the antibiotic in a normal host is 100%. The drug can be administered with or without meals. Food may slightly decrease the rate of absorption but has no effect on the amount of the drug absorbed. Linezolid shows a protein binding of only 31% and half-life of 5–7 hours. At a dosing schedule of 600 mg administered orally every 12 hours, the average steady-state plasma concentrations exceed MIC₉₀ concentrations for staphylococci, streptococci, and enterococci. It is primarily metabolized by oxidation of the morpholine ring, which produces two inactive metabolites. Its metabolism is unaffected by the cytochrome P450 enzyme system. Kinetics are similar in patients with mild to moderate renal or hepatic compromise. In patients over the age of 5, a dose of 10 mg/kg every 12 hours displays similar pharmacokinetic properties.²

In Vitro Activity

In vitro studies have shown linezolid to be effective against many antibiotic-resistant gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, and VRE.^{5–9} Linezolid is bacteriostatic against most susceptible organisms, but has shown bactericidal activity against *Clostridium perfringens*, *Bacteroides fragilis*, and some strains of *S. pneumoniae*.¹⁰ In addition to its coverage of antibiotic-resistant gram-positive organisms, it has some broad-spectrum activity against gram-positive cocci, gram-negative anaerobes, and some mycobacteria. It has also shown moderate in vitro inhibitory activity against *Haemophilus influenzae* and *Moraxella catarrhalis*, although it was not effective against Enterobacteriaceae and *Pseudomonas aeruginosa*.

In recent years, there has been a discovery of mutations that confer resistance to linezolid. A major mechanism that causes such resistance is mutation in various 23S rRNA nucleotides, which are organism specific. Organisms included are *Halobacterium halobium*, *Escherichia coli*, *Enterococcus faecalis*, *E. faecium*, *Mycobacterium smegmatis*, *Mycobacterium tuberculosis*, *S. aureus*, and *S. pneumoniae*. Another mechanism of resistance

Table 3.1 Novel Antibacterial Agents for Skin and Skin Structure Infections

Generic name	Brand name	Mechanism of action	Dosage	Skin infection usage
Linezolid	Zyvox	Binds to 23S portion of the 50S ribosomal subunit; prevents initiation complex formation	400–600 mg PO/IV q12 hours for 10–14 days	Uncomplicated/complicated
Tedizolid	Sivextro	Binds to the 50S bacterial ribosomal subunit, preventing initiation complex formation	200 mg QD × 6 days orally or as an IV infusion	Uncomplicated/complicated
Quinupristin/Dalfopristin	Synercid	Binds to different sites on the 50S subunit; inhibition of protein synthesis	7.5 mg/kg IV q12 hours for at least 7 days	Complicated
Daptomycin	Cubicin	Disrupts bacteria plasma membrane function	4 mg/kg IV q24 hours for 10–14 days	Complicated
Oritavancin	Orbactiv	Inhibits biosynthesis of cell wall peptidoglycan	1.5–3 mg/kg IV qD for 3–7 days	Complicated
Dalbavancin	Dalvance	Inhibits biosynthesis of cell wall peptidoglycan	500–1000 mg IV qweek	Complicated
Telavancin	Vibativ	Inhibits bacterial cell wall synthesis and disrupts membrane potential and permeability	10 mg/kg by IV infusion over 60 minutes every 24 hours for 4–14 days	Complicated
Moxifloxacin	Avelox	Inhibits DNA gyrase and topoisomerase IV	400 mg PO/IV qD for 7 days	Uncomplicated
Gatifloxacin	Tequin	Inhibits DNA gyrase and topoisomerase IV	400 mg PO/IV qD for 7–10 days	Uncomplicated
Tigecycline	Tygacil	Inhibits protein synthesis by blocking the 30S ribosomal subunit	Initial: 100 mg, then 50 mg BID IV over 30–60 minutes for 5–14 days	Complicated
Retapamulin	Altabax	Inhibits bacterial protein synthesis by interacting with the 50S ribosomal subunit	Topical application BID for 5 days	Uncomplicated (impetigo)
Ceftaroline	Teflaro	Inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins	600 mg q12 hours via IV infusion over 1 hour × 5–14 days	Complicated
Fosamil	—	Inhibits cell wall synthesis by binding to a highly conserved motif of lipid II and lipid III	TBD	TBD
Teixobactin	—			

is mutation of the ribosomal L3 protein, which is positioned on the 50S surface, but also extends into the protein initiation complex. Organisms associated with these mutations include *S. aureus*, *Staphylococcus cohnii*, and *Staphylococcus epidermidis*. Additionally, deletions of the L4 ribosomal protein have been shown to cause resistance in *S. pneumoniae* and *S. epidermidis*. This protein is positioned close to the translation complex, in the area where nascent peptides exit the ribosome. It has been noted that L3/L4 mutations have a lesser impact than 23S rRNA mutations.

Methylation is the only type of acquired antimicrobial resistance. Accordingly, some organisms acquire the multiresistance gene *cfr*, which encodes an rRNA methyltransferase. *Cfr* may be present on mobile genetic elements, such as plasmids and transposons, and is therefore capable of spreading resistance among pathogenic bacteria. This gene confers resistance to PhLOPS: phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin A antimicrobials.¹⁰

Clinical Indications

Currently linezolid is FDA approved for the treatment of various gram-positive infections, including both nosocomial and community-acquired pneumonias, complicated and uncomplicated skin and skin structure infections, and VRE infections.¹¹ Studies have been conducted comparing head-to-head, linezolid and standard antibiotic therapies in the treatment of skin and soft tissue infections. In terms of efficacy, a double-blind, randomized study in 332 adult patients with uncomplicated skin infections (cellulitis, skin abscesses, and furuncles)

secondary to staphylococcus and streptococcus compared linezolid 400 mg twice daily with clarithromycin 250 mg twice daily for a course of 7–14 days. Following treatment, 91% of the linezolid-treated patients had a clinical cure, compared to 93% in the clarithromycin group demonstrating that linezolid is as effective as clarithromycin.¹²

Another randomized, double-blind, multicenter trial compared the efficacy and safety of linezolid, an oxazolidinone, with those of oxacillin-dicloxacillin in patients with complicated skin and soft tissue infections.¹³ A total of 826 hospitalized adult patients were randomized to receive linezolid (600 mg intravenously) every 12 hours or oxacillin (2 grams intravenously) every 6 hours. Following sufficient clinical improvement, patients were switched to the respective oral agents, linezolid 600 mg orally every 12 hours, or dicloxacillin 500 mg orally every 6 hours. Primary efficacy variables were clinical cure rates in both the intent-to-treat (ITT) population and clinically evaluable (CE) patients and microbiological success rate in microbiologically evaluable (ME) patients. Safety and tolerability were evaluated in the ITT population. Demographics and baseline characteristics were similar across treatment groups in the 819 ITT patients. In the ITT population, the clinical cure rates were 69.8% and 64.9% in the linezolid and oxacillin-dicloxacillin groups, respectively ($P = .141$; 95% confidence interval -1.58 to 11.25). In 298 CE linezolid-treated patients, the clinical cure rate was 88.6%, compared with a cure rate of 85.8% in 302 CE patients who received oxacillin-dicloxacillin. In 143 ME linezolid-treated patients, the microbiological success rate was 88.1%, compared with a success rate of 86.1%

in 151 ME patients who received oxacillin-dicloxacillin. Both agents were well tolerated; most adverse events were of mild-to-moderate intensity. No serious drug-related adverse events were reported in the linezolid group.¹³

Linezolid was also found to be as effective as vancomycin in the treatment of skin and soft tissue MRSA infections.^{14,15} In VRE infections, a clinical success rate of 81% was noted indicating that treatment with linezolid may be superior to comparator antimicrobials in patients with complicated skin infections that also have comorbid conditions.¹⁶ There have been reports of development of resistance to linezolid in some patients with *E. faecium*.¹⁷

Dosage Regimens

The recommended dosage of linezolid depends on the severity of the skin or soft tissue infection:

1. Uncomplicated infections: 400 mg every 12 hours for 10–14 days
2. Complicated infections: 600 mg twice daily either via intravenous (IV) infusion or orally. Note that because the absolute bioavailability after oral dosing is nearly 100%, no dose adjustment is needed when switching from IV to oral therapy.⁴

Contraindications/Cautions

Linezolid is generally well tolerated with the most common adverse effects being diarrhea (8.3%), headache (6.5%), and nausea (6.2%).¹⁰ Because linezolid is a nonselective, reversible inhibitor of monoamine oxidase, it may interact with serotonergic or adrenergic agents.¹⁸ Like many other antimicrobials, it may cause pseudomembranous colitis, as a result of overgrowth of *Clostridium difficile*. Approximately 2% of patients develop thrombocytopenia, which appears to be dependent on duration of therapy. Elevated baseline creatinine levels and platelet count are also risk factors for development of thrombocytopenia.¹⁹

The effect is reversible; however, the manufacturer recommends monitoring patients with preexisting thrombocytopenia or patients whose treatment will exceed 2 weeks. No deaths related to thrombocytopenia have been reported.²

Linezolid has also been shown to cause lactic acidosis. A retrospective study of 72 patients treated for skin and soft tissue infections, bacteremia, and intraabdominal infections compared linezolid to teicoplanin use. No patients in the teicoplanin treatment group developed lactic acidosis, whereas 6.8% of the linezolid treatment group patients did. It was also shown that longer duration of linezolid use leads to lactic acidosis with higher anion gaps. Because lactic acidosis can be asymptomatic, serum lactate levels should be checked periodically for those patients on long-term use.²⁰ Additionally, there have been reports of optic neuropathy secondary to linezolid use, which is reversible upon discontinuation; therefore, it is also beneficial to monitor visual function in patients on long-term therapy.²¹

Conclusions

Linezolid is the first of a novel class of antimicrobials called oxazolidinones and is indicated for use in both uncomplicated and complicated skin and skin structure infections caused by MRSA or streptococcal species. Due to the rising prevalence of resistance, susceptibility testing can be done when considering this antimicrobial. With increasing knowledge of the linezolid

binding site, there is currently development of a new generation of oxazolidinones with improved defenses against the known resistance mechanisms.

Tedizolid

Tedizolid was approved in 2014 for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). Like linezolid, tedizolid is in the class of oxazolidinones. It appears to be advantageous over linezolid in terms of side effects, drug interactions, and resistance profile.

Mode of Action

Tedizolid phosphate is a prodrug that is converted to the active moiety tedizolid upon oral or IV administration. It binds to the 50S bacterial ribosomal subunit, which prevents the formation of a functional 70S initiation complex that is essential for the translation process and subsequently inhibits protein synthesis. It is bacteriostatic against enterococci, staphylococci, and streptococci.

In Vitro Activity

In vitro studies have demonstrated that tedizolid is 4- to 16-fold more potent than linezolid against staphylococci, streptococci, and enterococci. The MIC₉₀ is ≤0.5 µg/mL for gram-positives including MRSA, methicillin-sensitive *S. aureus* (MSSA), vancomycin-susceptible and -resistant enterococci, *S. pneumoniae*, *S. pyogenes*, *Streptococcus agalactiae*, anaerobic gram-positive bacilli, and *Clostridium* species.²²

The efficacy and safety of tedizolid compared to linezolid for the treatment of ABSSSI was evaluated in a multicenter, randomized, double-blind, double-dummy, noninferiority, phase 3 trial. Eligible patients were randomized to receive either tedizolid phosphate 200 mg PO once daily for 6 days or linezolid 600 mg PO twice daily for 10 days. MRSA was isolated in both tedizolid (41.1%) and linezolid (43.1%) treatment groups. Response rates were similar at the 48–72 hour assessment, with 79.5% in those taking tedizolid phosphate and 79.4% for linezolid. Gastrointestinal side effects occurred at a lower rate in the tedizolid treatment group, and those subjects also had a lower incidence of abnormal platelet count as compared to the linezolid treatment group.²³

Organisms resistant to oxazolidinones via mutations in genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally resistant to tedizolid as well. In a limited number of *S. aureus* strains tested, the presence of the *cfr* gene did not result in resistance to tedizolid in the absence of chromosomal mutations; therefore, it has significant potency advantage over linezolid-resistant strains carrying the horizontally transferable *cfr* gene.

Pharmacokinetics

Following multiple once daily oral or IV administrations, steady-state concentrations are achieved within 3 days, with tedizolid accumulation of approximately 30% (half-life of approximately 12 hours). The absolute bioavailability is 91%, and no dosage adjustment is necessary between IV and oral administration. Protein binding to human plasma proteins is 70%–90%. The mean steady-state volume of distribution in healthy adults following a single IV dose of 200 mg ranged from 67 to 80 L. Tedizolid penetrates into the interstitial space fluid of adipose and skeletal muscle tissue with exposure similar to free drug exposure in plasma.

Other than the active moiety tedizolid itself, there are no other metabolites. Tedizolid is not a substrate for hepatic CYP450 enzymes. Most of the elimination occurs via the liver, with 82% recovered in feces and 18% in urine as an inactive sulfate conjugate. More than 96% of the total elimination occurs within 96 hours. Less than 3% of the administered dose is excreted in feces and urine as unchanged tedizolid.

Clinical Indications

Tedizolid is indicated for the treatment of acute bacterial skin and skin structure infections, including cellulitis/erysipelas, wound infections, and cutaneous abscesses, that are caused by susceptible isolates gram-positive microorganism including *S. aureus* (MRSA and MSSA), *S. pyogenes*, *S. agalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*), and *E. faecalis*.

Dosage

Recommended dose: 200 mg once daily for 6 days either orally (with or without food) or as an IV infusion in patients 18 years of age or older.

No dose adjustment is necessary when changing from IV to oral form.

No dose adjustment is necessary for patients with hepatic impairment, renal impairment, or for patients on dialysis.

Contraindications/Cautions

There are no contraindications for using tedizolid. The safety and efficacy have not been studied in patients with neutropenia (<1000 cell/mm³), so alternative therapies should be considered. *C. difficile*-associated bacteria have been associated with its use. Common adverse events noted in phase 2 and phase 3 clinical trials include nausea, headache, diarrhea, vomiting, and dizziness.²⁴ It has also been associated with mild reversible inhibition of monoamine oxidase activity, reversible myelosuppression, serotonin syndrome, and peripheral and central neuropathies.²⁵

Conclusions

Tedizolid was designed to improve upon the oxazolidinones. Comparative studies confirm that tedizolid displays more potent activity against a broad range of gram-positive pathogens, including wild-type and linezolid-resistant strains, with a lower frequency of mutations leading to drug resistance. It is a promising drug for skin and skin structure infections caused by multidrug resistant pathogens, but additional data are needed on its safety when used in the setting of neutropenia and on coadministration with serotonergic agents.

Quinupristin/Dalfopristin

Quinupristin/dalfopristin is a combination of two semisynthetic pristinamycin derivatives, a 30:70 ratio, respectively, and is the first parenteral streptogramin antibacterial agent. Both quinupristin and dalfopristin have antibacterial capability individually but demonstrate synergistic activity when used in combination. Much of the clinical experience with this antibiotic is derived from five comparative trials and an FDA-sanctioned emergency-use program for patients without alternative therapies.

Mode of Action

Cellular Mechanism

Quinupristin and dalfopristin enter bacterial cells by diffusion and bind to different sites on the 50S ribosomal subunit resulting in an irreversible inhibition of bacterial protein synthesis.²⁶ Dalfopristin blocks the reaction catalyzed by the peptidyl transferase catalytic center of the 50S ribosome via inhibition of substrate attachment to the P-site and the A-site of the ribosome. Quinupristin inhibits peptide chain elongation. The synergistic effect of the combination appears to result from the fact that these compounds target early and late steps in protein synthesis.²⁷

Pharmacokinetics

Quinupristin/dalfopristin is rapidly cleared from the blood and is widely distributed to the tissues. It penetrates well in the liver, kidney, spleen, blood, bone marrow, salivary glands, adrenals, and the intestinal contents. It is eliminated via extensive metabolism to an active component in the liver via glutathione conjugation, and is excreted via bile into the feces²⁸; however, its clearance may be slightly reduced in patients with severe chronic renal failure. Its pharmacokinetics are unaffected by age or gender. Quinupristin has a half-life of approximately 1 hour, and dalfopristin has a half-life of approximately 30 minutes. The postantibiotic effect of the drug is prolonged to greater than 7.4 hours against streptococci regardless of penicillin susceptibility.²⁹ Quinupristin/dalfopristin inhibits the biotransformation rate of cytochrome P450 substrates in vitro.

In Vitro Activity

Quinupristin/dalfopristin has inhibitory activity against a broad spectrum of gram-positive bacteria including MRSA, vancomycin-resistant *Enterococcus faecium* (VREF), and drug-resistant *S. pneumoniae*. It is bactericidal against methicillin-resistant staphylococci and *S. pneumoniae* and bacteriostatic against most *Enterococcus faecium* in vitro. Quinupristin/dalfopristin also has demonstrated synergy with other antimicrobials. Rifampin is synergistic with quinupristin/dalfopristin against MRSA, and doxycycline is synergistic against VREF in vitro.

There have been limited reports of resistance to quinupristin/dalfopristin. In one such study, 70 VRE isolates were tested to assess for susceptibility to six different antimicrobials, including quinupristin/dalfopristin. 6.5% of *E. faecium* and 100% of the *E. faecalis* isolates were found to be resistant to the drug. Quinupristin/dalfopristin only has substantial activity against *E. faecium*.³⁰ *E. faecalis* is fully resistant to quinupristin/dalfopristin due to a gene-encoded efflux pump that reduces the intracellular concentration of the dalfopristin component.³¹

Clinical Indications

U.S. Food and Drug Administration (FDA) indications for quinupristin/dalfopristin are serious infections associated with VREF bacteremia and complicated skin and skin structure infections caused by methicillin-sensitive *S. aureus* or *S. pyogenes*. VREF infections are difficult to treat and few therapeutic options are currently available. These pathogens are resistant to most beta-lactam and aminoglycoside antimicrobials. Judicious use of vancomycin is currently being advocated to reduce the incidence of resistant organisms, but their presence continues. In 1995, quinupristin was approved for emergency use. During this emergency-use basis in the treatment of VREF infections, in which no other treatments were available, quinupristin/dalfopristin

had a 71% success rate³² and a significantly lower mortality rate than patients using other agents.³³ In another study, patients with complicated skin and skin structure infections who were administered quinupristin/dalfopristin had almost identical clinical success rates (68%) when compared to those using vancomycin, oxacillin, and/or cefazolin (71%).³⁴ In addition, in the treatment of patients with gram-positive nosocomial pneumonia, it was found to be equally as efficacious as vancomycin.³⁵

Dosage Regimens

Complicated skin or skin structure infections: 7.5 mg/kg intravenously over a 60-minute period twice daily for at least 7 days:

- Can be administered up to three times daily for bacteremic patients
- Dose adjustment to 5 mg/kg recommended for patients with hepatic insufficiency
- No dose adjustment needed for elderly or renally impaired patients

Contraindications/Cautions

Approximately 63% of patients receiving quinupristin/dalfopristin reported at least one adverse effect. Evaluation of these adverse effects is difficult, because they are often assessed in the context of severe underlying illnesses. Adverse venous events at the IV site of administration of the drug were the most common. Reports of pain and/or inflammation during its administration were reported in 34.9% to 74% of patients.^{34,36} Atrophy, edema, hemorrhage, hypersensitivity, burning, and thrombophlebitis were also reported. A statistically significant number of venous events occurred with quinupristin/dalfopristin compared with oxacillin, cefazolin, or vancomycin (66.2% versus 28.4%).³² Suggested but unproven management options to limit these events include administration in a larger volume of fluid, using a central venous catheter, and altering the infusion frequency to every 12 hours. Mild to moderate myalgias and/or arthralgias have been reported.³⁷ Gastrointestinal events also occurred with 4.6% experiencing nausea, 2.7% experiencing vomiting and diarrhea, and 2.5% developing a rash. The most common laboratory abnormalities reported were an increase in hepatic transaminases and bilirubin.³⁸ Use is contraindicated in patients with known hypersensitivity to streptogramins, or with any drugs metabolized by the CYP3A4 enzyme system (some anti-HIV agents, vinca alkaloids, benzodiazepines, immunosuppressives, corticosteroids, and calcium channel blockers). In addition, particular care should be taken when using medications that prolong the QT interval (e.g., astemizole, cisapride, disopyramide, lidocaine, quinidine, and terfenadine).³⁸ Caution is also recommended if using cyclosporin concomitantly.³⁹ As described above, resistance to quinupristin/dalfopristin has been encountered infrequently among vancomycin-resistant *E. faecium*, and resistance among staphylococci is rare in the United States.^{40,41}

Conclusions

Quinupristin/dalfopristin is the first parenteral streptogramin and offers a unique alternative treatment against multidrug resistant gram-positive bacteria. Due to its potency, bactericidal activity, long postantibiotic effect, and rare resistance, it has excellent potential for treatment of serious gram-positive infections; however, its efficacy should be weighed against possible adverse effects, tolerability, and interactions prior to utilizing

this potent antibiotic. In seriously ill patients with unresponsive infections and minimal other potential treatment options, it should be considered the treatment of choice.

Daptomycin

Daptomycin is a novel lipopeptide antibiotic derived from the fermentation of a strain of *Streptomyces roseosporus*. It has demonstrated potent antimicrobial activity against a wide variety of gram-positive bacteria including MRSA and VRE. Initially developed in the early 1980s, daptomycin was temporarily shelved due to concerns about skeletal muscle toxicity. At lower doses, this toxicity was not seen, but clinical trials using daptomycin were again halted due to treatment failures in patients with *S. aureus* endocarditis. Due to the need for new agents with activity against vancomycin-resistant bacteria, this IV therapy was reevaluated and now has supportive data from phase III clinical trials.⁴²

Mode of Action

Cellular Mechanism

The precise mechanism of action of daptomycin is unknown. Its activity depends on the presence of physiological levels of free calcium. It generally kills via insertion into and disruption of the functional integrity of the gram-positive plasma membrane, but does not enter the cytoplasm. This results in rapid loss of membrane potential,^{43,44} inhibition of lipoteichoic acid synthesis,^{45,46} cessation of macromolecular synthesis, and cell death.⁴⁷

Pharmacokinetics

Following once-daily dosing, it exhibits linear pharmacokinetics and minimal accumulation. It has a half-life of approximately 8.5 hours.⁴⁸ It is highly protein bound (94%), and its in vitro activity is altered in the presence of serum or albumin.^{49,50} Daptomycin is eliminated by the kidney, and therefore dose adjustments based on creatinine clearance are required. Because hepatic metabolism of daptomycin is limited, interactions with other drugs metabolized by the liver are minimal.

In Vitro Activity

It has rapid, concentration-dependent bactericidal activity against gram-positive organisms. Using the standard definition of a 3-log reduction in viable organisms, daptomycin, and not vancomycin, is bactericidal against both *S. aureus* and *E. faecalis*.⁵¹ In addition, in vitro studies designed to evaluate the bactericidal activity of daptomycin, compared to vancomycin, linezolid, and quinupristin-dalfopristin, against various gram-positive organisms found the bactericidal activity of daptomycin is improved when concentrations are equal to or greater than four times the minimal inhibitory concentration (MIC).⁵² At these levels, daptomycin and vancomycin achieved 99.9% killing of MRSA at 8 hours, which was greater than the killing seen with linezolid and quinupristin-dalfopristin. It also had greater activity against VRE at 8 and 24 hours, when compared to linezolid and quinupristin-dalfopristin. Spontaneous acquisition of resistance is rare as long as therapeutic serum levels of daptomycin are maintained. Synergistic interactions were noted most frequently with aminoglycosides and against enterococcal organisms.

There have been a few reports of MRSA nonsusceptibility to daptomycin. In one such report, daptomycin with rifampicin failed to treat a patient with prosthetic graft infection with

ST72-MRSA-IV, a strain that is predominantly found in Korea. Contributing factors to its failure could include insufficient dosage and preexisting resistance to rifampicin.⁵³ A study of daptomycin-resistant MRSA strains suggested that one mechanism of resistance may include overexpression and dysregulation of *dltA* transcription, which affects relative surface charge, but concluded that resistance is likely multifactorial and strain specific.⁵⁴

Clinical Indications

Daptomycin has been approved for the treatment of complicated skin and skin structure infections caused by gram-positive bacteria, including those caused by MRSA and MSSA (methicillin-susceptible *S. aureus*). In early phase II trials, the clinical efficacy of daptomycin was compared to conventional agents such as beta lactams, semisynthetic penicillins, and vancomycin for the treatment of skin infections and bacteremia.⁵⁵ In patients with skin and soft tissue infections, 2 mg/kg daily resulted in clinical cure or improvement in 29/30 patients, compared to 37/39 patients treated with conventional therapy. Two multicenter phase III trials have now been completed, involving a total of 1079 subjects with complicated skin and soft tissue infections.^{42,55} In both studies, patients were randomized for treatment with IV daptomycin (4 mg/kg, once daily) or standard treatment with a semisynthetic penicillin or vancomycin. Of all the clinically evaluable patients, 89% had clinical success with daptomycin, and 88% were treated successfully with standard treatment.⁴² These two groups were statistically equivalent. Of note, the group that received daptomycin required a significantly shorter course of treatment, with 63% of patients receiving daptomycin requiring only 4–7 days of treatment, while 67% of patients being treated with standard therapy requiring 8 or more days of treatment.⁴² Additionally, daptomycin is also approved for the treatment of right-sided endocarditis due to MSSA or MRSA.

Dosage Regimens

1. Recommended dosage: 4 mg/kg intravenously every 24 hours for 7–14 days.⁵⁶
2. Patients with creatinine clearance ≥ 30 mL/min: 4 mg/kg once every 24 hours
3. Patients with creatinine clearance ≤ 30 mL/min: 4 mg/kg once every 48 hours
 - Because daptomycin is eliminated primarily by the kidney, a dosage modification is recommended for patients with decreased creatinine clearance, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). When possible, daptomycin should be administered following hemodialysis on hemodialysis days.⁵⁷

Contraindications/Cautions

Daptomycin is well tolerated with an incidence and nature of serious adverse effects comparable to those seen with conventional therapy. The most frequently reported adverse events were headache and constipation in approximately 4% of patients. These events were not dose related and did not persist. There have also been a few reports of patients developing eosinophilic pneumonia. Although rare, this should be considered in patients who receive the drug and develop new pulmonary infiltrates.⁵⁸ Skeletal muscle has been identified as the primary target organ of daptomycin toxicity.⁵⁹ Reversible skeletal muscle toxicity occurred only at the highest dose tested (4 mg/kg every 12 hours). Transient muscle weakness and myalgia were noted,

but resolved 1 week after discontinuing daptomycin. In patients with renal impairment, both renal function and CPK should be monitored more frequently than once weekly. By monitoring CPK levels, muscle toxicity can be prevented, as CPK elevations precede muscle toxicity. No signs of cardiac or smooth muscle toxicity were noted. In addition, once-daily dosing has been shown to minimize associated muscle toxicity.

Conclusions

As resistance to conventional antimicrobials increases, daptomycin may be a useful adjunct to our antibiotic armamentarium. It possesses efficacy against resistant bacteria and provides for a rapid and concentration-dependent kill time, a broad spectrum of activity, and a low frequency of resistance.⁶⁰

Tigecycline

Tigecycline belongs to a novel class of antimicrobials called the glycylglycines. It was approved by the FDA in June 2005⁶¹ for the treatment of adults 18 years of age or older with complicated skin and skin structure infections caused by *E. coli*, *E. faecalis* (vancomycin-susceptible isolates only), *S. aureus* (methicillin-susceptible and -resistant isolates), *S. agalactiae*, *Streptococcus anginosus* group, *S. pyogenes*, and *B. fragilis*. It is also approved for the treatment of complicated intraabdominal infections caused by a variety of species.

Mode of Action

Cellular Mechanisms

Glycylglycines are semisynthetic derivatives of tetracycline antimicrobials in which a glycylamido moiety is attached at the nine position of the D-ring of the base molecule. This modification maintains the antibacterial effect but provides stability against mechanisms of tetracycline resistance.^{62,63} Specifically, it overcomes the action of ribosomal protection proteins and is not a substrate for tetracycline efflux pumps. It also overcomes other mainstream mechanisms of resistance, such as drug target modification, enzymatic degradation, and DNA gyrase mutations.⁶⁴ Like the tetracyclines, tigecycline is bacteriostatic and inhibits bacterial protein translation by binding to the 30S ribosomal subunit (although five times stronger than tetracycline) and blocks entry of amino-acyl tRNA molecules into the A site of the ribosome.⁶⁵

In Vitro Activity

Tigecycline shows broad-spectrum in vitro activity against gram-positive pathogens, including MRSA, VRE, methicillin-resistant *S. epidermidis*, and penicillin-resistant *S. pneumoniae*. Susceptible gram-negative organisms include *Acinetobacter baumannii*, *Moraxella catarrhalis*, *Stenotrophomonas maltophilia*, extended spectrum β -lactamase producing *E. coli*, *Klebsiella pneumoniae*, and anaerobes. Tigecycline is also effective against atypical pathogens such as *M. pneumoniae*, *Legionella* spp., *Mycoplasma hominis*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, and rapidly growing mycobacteria.⁶⁵ It is not active against *Pseudomonas*, *Proteus*, *Providencia*, or *Morganella* spp. These drugs most commonly confer resistance via drug recognition and efflux by RND family transporters.

Pharmacokinetics

In healthy subjects given IV tigecycline, peak concentration is linearly proportional to dose over the range of 12.5–300 mg. Approximately 71%–89% of tigecycline is bound to plasma

proteins. Following IV administration, tigecycline serum concentrations initially decline rapidly during distribution into body tissues.²⁵ The mean half-life of tigecycline after a single 100-mg dose was 27.1 hours; after multiple dosing of 50 mg every 12 hours, the mean half-life was 42.4 hours.¹ Approximately 59% of the drug is eliminated by biliary/fecal excretion, and 33% is excreted in urine. Of the total dose, approximately 22% is excreted as unchanged tigecycline in urine. Also of note, tigecycline does not interfere with common cytochrome P450 enzymes, making drug interactions uncommon.

Clinical Indications

Tigecycline is indicated for complicated skin and soft tissue infections as well as for complicated intraabdominal infections. It is also clinically indicated for community-acquired bacterial pneumonia, health care-associated pneumonia, and bacteremia. Its efficacy as monotherapy was demonstrated to be similar to combination therapy with vancomycin and aztreonam in two double-blind phase 3 comparison studies. Patients (total = 1116) with cSSTI received tigecycline (100 mg, followed by 50 mg intravenously twice daily) or vancomycin (1 g intravenously twice daily) plus aztreonam (2 g intravenously twice daily) for up to 14 days. Clinical responses to tigecycline and vancomycin-aztreonam at test-of-cure were similar: 79.7% (95% confidence interval [CI], 76.1%–83.1%) versus 81.9% (95% CI, 78.3%–85.1%) ($P = .4183$). Adverse events were similar, with increased nausea and vomiting in the tigecycline group and increased rash and elevated hepatic aminotransferase levels in the vancomycin-aztreonam group.⁶⁶

Its efficacy as monotherapy (100 mg, followed by 50 mg q12h) was also demonstrated to be similar to combination therapy with imipenem-cilastatin (500 mg q6h) in two phase 3 double-blind, randomized trials that treated patients with complicated intraabdominal infection. Clinical cure rates were 86% in both treatment groups. Bacterial eradication by tigecycline and imipenem-cilastatin was also similar at 86% and 87% for *E. coli*, and 78% and 95% for *B. fragilis* and *C. perfringens*, respectively.

Dosage Regimens

1. Recommended initial dose: 100 mg, followed by 50 mg every 12 hours.
 - a. IV infusions should be administered over 30–60 minutes every 12 hours.
 - b. The recommended duration of treatment for cSSTI or for complicated intraabdominal infections is 5–14 days.
 - c. No dose adjustment is made in patients with mild-moderate hepatic impairment.
2. Initial dose with severe liver disease: 100 mg, followed by 25 mg every 12 hours.
 - a. No adjustment is necessary with renal disease or in patients on hemodialysis.
 - *The safety and efficacy have not been tested in patients younger than 18 years old.*⁶⁵

Contraindications/Cautions

In phase 3 clinical studies with 1415 patients, the most commonly reported adverse events were nausea (29.5%) and vomiting (19.7%). Nausea and vomiting generally occurred within the first 2 days of treatment. Only 1.3% of patients discontinued

therapy due to nausea and 1% due to vomiting.⁶⁵ Diarrhea was also reported in 13% of patients in phase 3 clinical trials but did not test positive for *C. difficile* toxin.

Laboratory abnormalities reported during tigecycline treatment included increased PT/PTT, without significant bleeding episodes, increased BUN without concomitant nephrotoxicity or rise in creatinine, and hyperbilirubinemia. While in phase 3 clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with tigecycline (6.7%) versus comparators (4.6%), the relationship of this outcome to treatment cannot be established due to differences between treatment groups at baseline.

Glycylglycines are structurally similar to tetracyclines and, therefore, may have similar adverse events such as photosensitivity, pseudotumor cerebri, pancreatitis, vertigo, and hearing loss. Patients with a history of tetracycline hypersensitivity should be closely monitored if treated with tigecycline. Skin reactions are uncommon, but include pruritus, urticaria, and maculopapular rash. Tigecycline may cause fetal harm if administered to pregnant women and may cause permanent tooth discoloration during development. It should not be administered simultaneously with amphotericin B or diltiazem. Coagulation studies should be monitored in patients on warfarin and tigecycline.⁶⁷

Conclusions

Tigecycline monotherapy is as effective as combination therapy with vancomycin and aztreonam in the treatment of cSSTI. This new agent thus holds promise as an alternative to the beta-lactams and fluoroquinolones for the initial empiric treatment of serious dermatologic infections.⁶⁸

Retapamulin

Retapamulin is an antibiotic ointment approved in April 2007 for the treatment of impetigo due to MSSA and *S. pyogenes*. It is a semisynthetic derivative of the compound pleuromutilin, which is isolated through fermentation of the fungus *Clitopilus scyphoides*, an edible mushroom.⁶⁹

Mode of Action

Cellular Mechanisms

Retapamulin selectively inhibits bacterial protein synthesis by interacting with the ribosomal 50S subunit L3 protein to inhibit peptidyl transfer, block P-site interactions, and prevent the normal formation of active 50S ribosomal subunits.⁷⁰

In Vitro Activity

Retapamulin is bacteriostatic against *S. aureus* and *S. pyogenes* at the retapamulin in vitro minimum inhibitory concentration (MIC) for these organisms. At concentrations 1000× the in vitro MIC, retapamulin is bactericidal against these same organisms. It is also effective against *S. agalactia*, B hemolytic streptococci, *Streptococcus viridans*, and coagulase-negative staphylococci. Retapamulin also has in vitro activity against anaerobes, as demonstrated in a study of 232 anaerobic isolates in which <2 mg/L retapamulin was able to inhibit 90% of these isolates.⁷¹

Retapamulin demonstrates no in vitro target-specific cross-resistance with other classes of antimicrobials. Two mechanisms that cause reduced susceptibility to retapamulin identified in vitro are mutations in ribosomal protein L3 or the presence of an efflux mechanism. Decreased susceptibility

of *S. aureus* to retapamulin (highest retapamulin MIC was 2 mcg/mL) develops slowly in vitro via multistep mutations in L3 after serial passage in subinhibitory concentrations.⁷⁰ Despite the fact that it is not approved for MRSA, studies have shown the superiority of retapamulin's resistance profile over mupirocin. In a study evaluating the efficacy of retapamulin and six other antimicrobials against 155 MRSA isolates, resistance occurred in 2.6% of retapamulin-treated isolates and 10% of mupirocin-treated isolates. In fact, retapamulin maintained good activity against 94% (15/16) of mupirocin-resistant isolates.⁷²

Pharmacokinetics

Systemic exposure following topical application of retapamulin through intact and abraded skin was low. In a study of healthy adults, applying retapamulin ointment, 1%, once daily to intact skin (800 cm²) and abraded skin (200 cm²) under occlusion for up to 7 days, provided a median C_{max} plasma value at day 7 of 3.5 ng/mL (range, 1.2–7.8 ng/mL) from intact skin and 9 ng/mL (range, 6.7–12.8 ng/mL) from abraded skin. Retapamulin is 94% bound to human plasma proteins regardless of concentration. Metabolism takes place mainly in the liver by mono-oxygenation and N-demethylation, and the major enzyme responsible for this is cytochrome P450 3A4. The apparent volume of distribution and retapamulin elimination in humans has not been investigated due to low systemic exposure after topical application.⁷³

Clinical Indications

Retapamulin ointment is indicated for use in adults and pediatric patients aged 9 months and older for the topical treatment of impetigo (up to 100 cm² in total area in adults or 2% total body surface area in pediatric patients aged 9 months or older) due to MSSA or *S. pyogenes*.⁶⁹ In Europe, it is also approved for infected lacerations, abrasions, sutured wounds without abscesses, and infected atopic dermatitis.

Retapamulin ointment has been studied in a multicenter, randomized, double-blind, placebo-controlled parallel-group study of adult and pediatric (aged 9 months or older) patients applying retapamulin ointment twice daily for 5 days for the treatment of impetigo. Of the 210 patients enrolled, 164 (78%) were younger than 13 years. Clinical success was defined as the absence of treated lesions, treated lesions that had become dry without crusts or without erythema compared with baseline, or treated lesions that improved such that no further antimicrobial treatment was required. At 2 days posttreatment, the intent-to-treat clinical population for retapamulin showed a success rate of 85.6% (119 of 139 patients) compared with the placebo group, which had a success rate of 52.1% (37 of 71 patients). A follow-up examination 9 days after treatment showed a similar trend: retapamulin had a success rate of 75.5% (105 of 139 patients) and a placebo rate of 39.4% (28 of 71 patients).⁷⁴

Retapamulin has also been shown to be superior to sodium fusidate for the treatment of impetigo. A randomized, observer-blinded, phase III study of 519 adult and pediatric (≥9 months) subjects with impetigo were treated with retapamulin ointment, 1% (BID for 5 days) or with sodium fusidate ointment 2% (TID for 7 days). Both were well tolerated, but retapamulin had a clinical efficacy of 99.1% versus only 94% for fusidic acid.⁷⁵ There have been no comparative clinical studies with any other topical antibiotic such as mupirocin.

Dosage

Recommended dose: Apply a thin layer to the affected area twice a day for 5 days:

- Up to 100 cm² in total area in adults
- 2% total body surface area in pediatric patients aged 9 months or older

Retapamulin is dispensed as a 1% ointment in 5, 10, and 15 gram tubes. To reduce the development of drug-resistant bacteria and maintain the efficacy of retapamulin, use should be limited to treatment or prevention of infections that are proven or strongly suspected to be caused by susceptible bacteria.⁶⁹

Contraindications/Cautions

Retapamulin ointment is pregnancy category B, therefore it should only be used in pregnancy when the potential benefits outweigh the risks and at the discretion of the prescribing physician.

Long-term studies in animals to evaluate carcinogenic potential have not been performed with retapamulin. It has shown no genotoxicity, and no evidence of impaired fertility has been found in both male and female rat studies.

The safety of retapamulin ointment has been assessed in a study of 2115 adult and pediatric patients who used at least one dose from a 5-day, twice-daily regimen. Adverse events rated by the investigator as drug related occurred in 5.5% (116 of 2115) of patients treated with retapamulin ointment, the most common of which was application site irritation (1.4%). There are limited reports of contact dermatitis development secondary to retapamulin application, all of which resolved upon discontinuation. A safety profile has not been established for patients younger than 9 months.⁶⁹

Due to low systemic exposure to retapamulin following topical application in patients, dosage adjustments for retapamulin are unnecessary when coadministered with CYP3A4 inhibitors, such as ketoconazole. Based on in vitro P450 inhibition studies and the low systemic exposure observed following topical application, retapamulin is unlikely to affect the metabolism of other P450 substrates. The effect of concurrent application of other topical products to the same area of skin has not been studied.⁶⁹

Ceftaroline Fosamil

Ceftaroline is an advanced, fifth-generation cephalosporin that was first approved in October 2010. It is available for the treatment of acute bacterial skin and skin structure infections, as well as community-acquired pneumonia. Ceftaroline is unique in that unlike other cephalosporins, it is active against MRSA, but like later generation cephalosporins, it retains activity against gram-negatives.

Mode of Action

Cellular Mechanism

Ceftaroline acts by inhibiting bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs) 1–3. This blocks the final transpeptidation step of peptidoglycan synthesis and inhibits cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysis and murein hydrolases) while cell wall assembly is arrested. Of note, ceftaroline has a strong affinity for PBP2a, a modified PBP

in MRSA, and PBP2x in *S. pneumoniae*, which contributes to its spectrum of activity against these bacteria.

In Vitro Activity

Ceftaroline has potent in vitro activity against multidrug resistant strains of *S. pneumoniae*. The MIC₉₀ for most isolates is ≤ 0.5 mg/L (range ≤ 0.003 –2 mg/L). Its activity has been compared with ceftriaxone against penicillin-, cephalosporin-, and levofloxacin-resistant *S. pneumoniae*. The MIC₉₀ values of ceftaroline are at least two double dilutions less than ceftriaxone. Ceftaroline also has in vitro activity against MRSA, in which most isolates studied have been inhibited by MIC₉₀s of ≤ 1 mg/L (range ≤ 0.12 –2 mg/L). Similarly, MIC₉₀s for hVISA, VISA, and VRSA have shown to be ≤ 2 mg/L (range ≤ 0.25 –4 mg/L).⁷⁶

The FOCUS trials were two double-masked, randomized, active comparator-controlled trials to evaluate the safety and efficacy of ceftaroline fosamil 600 mg IV every 12 hours compared to ceftriaxone 1 g IV every 24 hours for 5–7 days for admitted patients with CABP. Patients with suspected MRSA infection were excluded. Ceftaroline displayed a higher clinical cure rate of 85.1% versus 75.5% for ceftriaxone. Cure rates against *S. pneumoniae*, MDRSP, and *S. aureus* favored ceftaroline, and were similar to ceftriaxone for gram-negative pathogens. Clinical cure rates for bacteremia were 71.4% and 58.8% for ceftaroline and ceftriaxone, respectively. Relapse rates were similar at the follow-up visit with 1.9% for the ceftaroline treatment group and 1.2% for the ceftriaxone treatment group.

The CANVAS trials were multinational, multicenter, phase 3, double-masked, randomized, active comparator-controlled trials to evaluate the safety and efficacy of ceftaroline fosamil 600 mg IV every 12 hours compared with a combination of vancomycin 1 g every 12 hours plus aztreonam 1 g every 12 hours IV for 5–14 days for the treatment of ABSSSI. Clinical cure rates were 92.7% and 94.4% for the ceftaroline and combination group, respectively. Bacteremia cure rates were 84.6% and 100%, respectively. Clinical relapse rates were similar at the follow-up visit: 1.1% for ceftaroline, and 0.9% for combination treatment group.⁷⁷

Pharmacokinetics

Ceftaroline fosamil is an inactive prodrug that undergoes rapid conversion to the bioactive ceftaroline in plasma via phosphatases. The volume of distribution ranges from 18.3 to 21.6 L. It exhibits approximately 20% protein binding. The half-life elimination time is 2.7 hours, and the time to peak is 1 hour. It is not a substrate for CYP450 enzymes, indicating minimal potential for drug interactions. Hydrolysis of the beta-lactam ring of ceftaroline forms the inactive, open-ring metabolite ceftaroline M-1. Ceftaroline and its metabolites are primarily eliminated by the kidneys, and dose adjustments must be made for patients with renal impairment. Following a 600 mg IV dose, 88% is recovered in the urine and 6% in the feces within 48 hours.⁷⁸

Clinical Indications

Ceftaroline is indicated for the treatment of acute bacterial skin and skin structure infections caused by susceptible isolates of gram-positive and gram-negative microorganisms that included *S. aureus* (MRSA and MSSA), *S. pyogenes*, *S. agalactiae*, *E. coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. It is also indicated for the treatment of community-acquired bacterial

pneumonia caused by susceptible isolates gram-positive and gram-negative microorganisms including *S. pneumoniae* (including cases with concurrent bacteremia), *S. aureus* (MSSA isolates only), *H. influenzae*, *K. pneumoniae*, *K. oxytoca*, and *E. coli*.

Dosage

1. Recommended dose: 600 mg every 12 hours by IV infusion over 1 hour in patients 18 years of age and older
2. Recommended duration: 5–14 days for ABSSSI versus 5–7 days for CABO
3. Dosage for patients with renal impairment with CrCl < 50 mL/min
CrCl > 30 to ≤ 50 : 400 mg IV over 1 hour every 12 hours
CrCl ≥ 15 to ≤ 30 : 300 mg IV over 1 hour every 12 hours
End-stage disease and hemodialysis: 200 mg IV over 1 hour every 12 hours

Contraindications/Cautions

Ceftaroline is contraindicated in patients with known serious hypersensitivity to ceftaroline or other cephalosporins, because anaphylaxis and anaphylactoid reactions have been reported. Precautions include hypersensitivity reactions, *C. difficile*-associated diarrhea, and direct Coombs test seroconversion from a negative to a positive result.

In the pooled analysis of four controlled, comparative phase 3 clinical trials including 1300 patients treated with ceftaroline, serious adverse events occurred in 7.5%. The more common adverse effects include diarrhea, nausea, and rash.

Conclusions

Ceftaroline is a well-tolerated treatment for resistant gram-positive and common gram-negative infections. Its efficacy is similar to comparator agents in the treatment of ABSSSI and CABP. Its lack of activity against resistant gram-negative pathogens limits its current use as a monotherapeutic agent, but adding on a β -lactamase inhibitor may allow its activity to be extended.

ANTIMICROBIALS IN DEVELOPMENT

Oritavancin, dalbavancin, and telavancin are novel semisynthetic glycopeptide antimicrobials, belonging to the same class as vancomycin. The antibacterial activity of glycopeptide antimicrobials results from the inhibition of bacterial cell wall formation. More specifically, these antimicrobials inhibit the biosynthesis of bacterial cell wall peptidoglycan. These agents are currently in late stages of clinical development.

Oritavancin

Oritavancin is distinguished from vancomycin by its bactericidal activity against enterococci, *S. pneumoniae*, and staphylococci, including MRSA.^{60,79,80} It differs from vancomycin by the presence of a hydrophobic 4'-chlorobiphenylmethyl group on the disaccharide sugar, the addition of a 4-epi-vancosamine monosaccharide to the amino acid residue in ring 6, and replacement of the vancosamine moiety by 4-epi-vancosamine. It has multiple mechanisms of action that confer activity against vancomycin-resistant and -susceptible pathogens, and has rapid, concentration-dependent killing against actively growing, stationary, and biofilm producing gram-positives.⁸¹

Mode of Action

Cellular Mechanism

Oritavancin's major mechanisms of action include inhibition of transglycosylation (polymerization) of cell wall synthesis, inhibition of transpeptidation (cross-linking) of cell wall synthesis, and cell membrane disruption. Specifically, it inhibits transglycosylation that is needed for peptidoglycan synthesis by binding to the D-alanyl-D-alanine stem terminus, similar to vancomycin. Unlike vancomycin, it binds to the pentaglycyl (Asp/Asn) bridging segment in peptidoglycan. The hydrophobic 4'-chlorobiphenylmethyl group allows for disruption of the cell membrane that causes increased permeability, depolarization, and cell death.

In Vitro Activity

In a study of oritavancin activity tested against 15,764 gram-positive isolates, it was shown to have substantial activity against all pathogens, regardless of their resistance profile. The maximum MIC against all staphylococci tested was 4 µg/mL. The MIC₉₀ against *S. aureus* was 0.12 µg/mL, and 0.06 and 0.12 against *E. faecalis* and *E. faecium*, respectively. It was also active against GRE, with MIC₉₀ of 0.25 and 1 µg/mL against VanA strains and of *E. faecium* and *E. faecalis*, respectively. Oritavancin showed potent activity against streptococci; MIC_{90s} for different streptococcal species ranged from 0.008 to 1 µg/mL.⁸²

In animal studies using rabbits as models, oritavancin was successful in the treatment of endocarditis from MRSA.⁸³ It also has a longer half-life (over 10 days) than vancomycin, and thus can potentially offer a shorter duration of treatment.⁸⁴ In a phase III study, IV oritavancin (either 1.5 mg/kg or 3 mg/kg once daily) followed by placebo was compared to IV vancomycin (15 mg/kg once daily) followed by oral cephalexin in 517 patients with complicated skin and soft tissue infections (unpublished data).⁸⁵ Efficacy was statistically equivalent in the two groups, with a 76% clinical success rate in the group that received oritavancin and 80% in patients who received vancomycin/cephalexin. Patients in the oritavancin group required an average of only 5.7 days of treatment in those receiving the 1.5 mg/kg/d dosage, and 5.3 days of treatment for the 3 mg/kg/d group, compared to 11.5 days in patients receiving vancomycin/cephalexin.⁸⁵

A second phase 3, double-blind, randomized trial in 1246 patients with complicated skin and soft tissue infections corroborated that oritavancin 200 mg daily for 3–7 days IV followed by oral placebo was as effective as 10–14 days of vancomycin/cephalexin (vancomycin/cephalexin at 15 mg/kg twice daily for 3–7 days IV followed by 1000 mg twice daily oral cephalexin). This study also demonstrated that significantly fewer patients experienced adverse events ($P < .001$) and fewer patients discontinued therapy ($P = .003$) in the oritavancin group than in the vancomycin/cephalexin group.⁸⁶

Pharmacokinetics

Oritavancin is approximately 85% bound to human plasma proteins. The population mean total volume of distribution is approximately 87.6 L, indicating that it is extensively distributed into the tissues. Oritavancin is not metabolized. In humans, oritavancin is slowly excreted unchanged in feces and urine with less than 1% and 5% of the dose recovered in feces and urine, respectively, after 2 weeks of collection. Oritavancin has a terminal half-life of approximately 245 hours and a clearance of 0.445 L/h based on population pharmacokinetic analyses.

Oritavancin has been shown to inhibit the activities of cytochrome P450 enzymes 1A2, 2B6, 2D6, 2C9, 2C19, and 3A4.

This observed inhibition of multiple CYP isoforms in vitro is likely to be reversible and noncompetitive. In vitro studies indicate that oritavancin is neither a substrate nor an inhibitor of the efflux transporter P-glycoprotein (P-gp). Additionally, oritavancin is a weak inducer of CYP3A4 and CYP2D6. Because it is a weak inhibitor of CYP2C19 and CYP2C9, one must be aware of possible interactions with drugs that use these same enzymes for metabolism, such as midazolam, dextromethorphan, and omeprazole.⁸⁷

Clinical Indications

Oritavancin was approved in 2014 for treatment of adults 18 years of age and older with acute bacterial skin and skin structure infections, caused by susceptible isolates of the following gram-positive organisms: *S. aureus* (MSSA and MRSA isolates), *S. pyogenes*, *S. agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), and *E. faecalis* (vancomycin-susceptible isolates only).⁸⁸

Dosage

Recommended dose: single 1200 mg intravenous infusion over 3 hours in patients 18 years of age and older

No dose adjustment is needed for patients with mild-moderate renal or hepatic impairment. The safety and efficacy in patients under the age of 18 have not been studied.

Contraindications/Caution

Besides known hypersensitivity to oritavancin, the only other contraindication is the use of IV unfractionated heparin sodium within 48 hours of treatment, because aPTT test results are expected to remain falsely elevated for 48 hours after giving oritavancin.

Oritavancin should only be used in patients on chronic warfarin therapy when the benefits outweigh the risks due to higher exposure to warfarin that may increase the risk of bleeding.

Some rare, adverse reactions reported with oritavancin use include infusion-related reactions (pruritis, urticaria, flushing), *C. difficile*-associated diarrhea, and osteomyelitis.⁸⁷

Dalbavancin

Dalbavancin has also been shown to be bactericidal in vitro studies with gram-positive pathogens.⁸⁹ It is a long-acting agent administered once weekly and is highly potent against the common species associated with SSSI, including many antimicrobial-resistant strains. It is bactericidal in vitro against *S. aureus* and *S. pyogenes* at concentrations similar to what is achieved by the recommended dosage regimen.

Mode of Action

Cellular Mechanism

Dalbavancin interferes with cell wall synthesis by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in nascent cell wall peptidoglycan, which prevents cross-linking.

In Vitro Activity

Dalbavancin's in vitro activity against 81,673 isolates of staphylococci, enterococci, and streptococci has been evaluated. The MIC₉₀ for *S. aureus* is 0.06 µg/mL. It is 16-fold more active than vancomycin (MIC₉₀ 1 µg/mL) against both oxacillin-susceptible

and -resistant *S. aureus* isolates. MIC₉₀s for *E. faecalis* and *E. faecium* are 0.06 and 0.12, respectively, but it is less active against vancomycin-resistant strains. β -Hemolytic and viridians group streptococci were very susceptible to dalbavancin with an MIC₉₀ \leq 0.03 μ g/mL. Overall, dalbavancin was \geq 16-fold more active than vancomycin against the analyzed gram-positive species.⁹⁰

In initial animal studies using rats, dalbavancin successfully treated lobar pneumonia from penicillin-resistant pneumococci.⁴¹ In a phase I study with healthy volunteers, subjects received single IV infusions of dalbavancin in doses ranging from 70 to 360 mg.⁸⁹ Other subjects received dosages of 70 mg per day for 7 days. All single and multiple dosages studied were well tolerated. Dalbavancin was also found to have a long half-life of approximately 10 days. These results suggest that once weekly dosing could be sufficient to provide trough concentrations that are bactericidal for staphylococcus.⁸⁹

This was followed by a phase II trial with 62 patients with skin and soft tissue infections. Patients were treated with one of two dalbavancin dosing regimens compared to a standard of care antibiotic.⁹¹ Clinical success rates were 94.1% in patients receiving two doses of dalbavancin, given 1 week apart, 76.2% for standard of care treatment (dosing was daily for 7–21 days), and 64.3% for the group that received a single dose of dalbavancin (unpublished data).⁹¹

In a randomized, double-blind phase 3 noninferiority study, two doses of dalbavancin (1000 mg given on day 1 followed by 500 mg given on day 8) were as well tolerated and as effective as linezolid given twice daily for 14 days for the treatment of patients with complicated SSSI, including those infected with MRSA.⁹²

DISCOVER 1 and DISCOVER 2 were two major double-blind, international, multicenter, randomized trials that took place between 2011 and 2012. Eligible patients were required to have cellulitis, a major abscess, or a wound infection. The first treatment group received 1 g dalbavancin given intravenously over 30 minutes on day 1, followed by 500 mg given intravenously over 30 minutes on day 8. The other treatment group received 1 g vancomycin intravenously over 120 minutes every 12 hours for at least 3 days, with an option to switch to oral linezolid, 600 mg every 12 hours, to complete 10–14 days of therapy. The results were promising. In DISCOVER 1, an early clinical response occurred in 240 of 288 patients (83.3%) receiving dalbavancin and 233 of 285 (81.8%) receiving vancomycin-linezolid. In DISCOVER 2, the early clinical responses were 76.8% and 78.3%, respectively. Dalbavancin was successful in 89.2% of patients with MRSA infection and in 91.5% of those with MSSA infection. Also of note, there were fewer adverse events reported in the dalbavancin treatment group.⁹³

Pharmacokinetics

Dalbavancin is reversibly bound to human plasma proteins, primarily to albumin. Plasma protein binding is 93%, and is not altered by drug concentration, renal impairment, or hepatic impairment. In vitro studies indicate that dalbavancin is not a substrate, inhibitor, or inducer of CYP450 isoenzymes, making drug interactions less likely. Following administration of a single 1000 mg dose in healthy subjects, 20% of the dose was excreted in feces through 70 days postdose. An average of 33% was excreted in urine as unchanged dalbavancin, and 12% was excreted in urine as the metabolite hydroxy-dalbavancin through 42 days postdose.⁹⁴

Clinical Indications

Dalbavancin is approved for the treatment of acute bacterial skin and skin structure infections in adults caused by the following gram-positive organisms: *S. aureus* (including MSSA and MRSA), *S. pyogenes*, *S. agalactiae*, and *Streptococcus anginosus* group (*S. anginosus*, *S. intermedius*, *S. constellatus*).⁹⁴

Dosage

Recommended two-dose regimen: 1000 mg followed by 500 mg 1 week later

- Administer via intravenous infusion over 30 minutes.⁹⁴

Contraindications/Cautions

Dalbavancin is only contraindicated in patients with a known hypersensitivity to the drug. Precautions include hypersensitivity and skin reactions, infusion-related reactions that resemble Red Man Syndrome, ALT elevation, and *C. difficile*-associated diarrhea.

The adverse reactions of 1778 patients treated with dalbavancin in seven phase 2 and 3 clinical trials were analyzed. It was found that the most common reactions were nausea, headache, and diarrhea.⁹⁴

Telavancin

Telavancin is another lipoglycopeptide antibiotic that exerts concentration-dependent bactericidal activity. It has potent activity against a variety of gram-positive organisms, including *S. aureus* (MRSA, hVISA, VISA), coagulase negative staphylococci, *Streptococcus* species, and many gram-positive anaerobes. It is also active against VAN-susceptible and VanB VAN-resistant enterococci. It has great potential for replacing vancomycin for MRSA infections but should be used with caution due to nephrotoxicity.

Mode of Action

Cellular Mechanism

Telavancin has a dual mechanism. First, it inhibits bacterial cell wall synthesis by binding to D-Ala-D-Ala, thereby blocking polymerization and cross-linking of peptidoglycan. Unlike vancomycin, it also disrupts membrane potential and changes cell permeability due to its lipophilic side-chain moiety.

In Vitro Activity

Telavancin is active against gram-positive aerobes and anaerobes. It is active against MSSA and MRSA with a MIC of 0.12–2 and 0.06–2 mg/L, respectively. Activity against vancomycin-susceptible *E. faecium* and *E. faecalis* is also present, with MICs of 0.015–0.5 and 0.06–2 mg/L, respectively. It displays some activity against VRE, with a MIC of 0.025–6 mg/L for vancomycin-resistant *E. faecalis*, and a MIC of 0.015–16 mg/L for vancomycin-resistant *E. faecium*. The MIC₉₀ for 29 isolates of vancomycin-resistant *E. faecalis* and 29 isolates of vancomycin-resistant *E. faecium* is more than 64 times lower than that of vancomycin. Telavancin also has good activity against streptococci, including those that are multidrug resistant. Activity against other pathogens includes VISA and hVISA, *B. anthracis*, and *Listeria*.⁹⁵

In a systemic review analyzing six randomized controlled studies that compared telavancin to vancomycin, telavancin was shown to be noninferior for the treatment of MRSA infections. Telavancin showed higher eradication rates (OR = 1.71

[1.08–2.70]) and better clinical response (OR = 1.55 [0.93–2.58]). Regarding hospital-acquired pneumonia, telavancin was also noninferior to vancomycin in its clinical response in two phase III RCTs. Mortality rates for the pooled trials were comparable with 20% and 18.6%, respectively, for telavancin and vancomycin. Pooled data from cSSTIs and HAP studies using telavancin 10 mg/kg indicated higher rates of increased serum creatinine, serious adverse events, and adverse event-related withdrawals.⁹⁶

Pharmacokinetics

Telavancin has a half-life of 8 hours. It has 90% binding to human plasma proteins, primarily to albumin, in a concentration-independent manner. Binding is not affected by renal or hepatic impairment. No metabolites were detected in in vitro studies. CYP 450 enzymes were not shown to participate in its metabolism. Clearance is not altered by inhibitors of any of these enzymes. Telavancin is primarily eliminated by the kidney, with 76% excretion via urine and <1% via feces.

Telavancin has been shown to have inhibitory activity against CYP 1A2, 2C9, 2C19, 2D6, and 3A4/5. Further studies have shown that there are no significant drug interactions with other major CYP 3A substrates, midazolam, aztreonam, or piperacillin-tazobactam.

Clinical Indications

Telavancin is approved for complicated skin and skin structure infections, specifically those caused by susceptible gram-positive organisms including methicillin-susceptible or -resistant *S. aureus*, vancomycin-susceptible *E. faecalis*, *S. pyogenes*, *S. agalactiae*, or *Streptococcus anginosus* group. It is also approved for hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible isolates of *S. aureus* when alternate treatments are not appropriate.⁹⁷

Dosage

1. Complicated skin and skin structure infections: 10 mg/kg by IV infusion over 60 minutes every 24 hours for 4–14 days
 - a. Requires dosage adjustment in patients with renal impairment: suggesting dosing is 7.5 mg/kg every 24 hours for a CL_{cr} of 30–50 mL/min and 10 mg/kg every 48 hours for a CL_{cr} of <30 mL/min.
2. Hospital-acquired and ventilator-associated bacterial pneumonia: 10 mg/kg by IV infusion over 60 minutes every 24 hours for 7–21 days
 - a. Requires dosage adjustment in patients with renal impairment⁹⁷

Contraindications/Precautions

The only contraindication to using telavancin is when there is known hypersensitivity to it. Warnings include hypersensitivity

reactions, infusion reactions, *C. difficile*-associated diarrhea, QTc prolongation, coagulation test interference, and nephrotoxicity. In fact, it is recommended to monitor renal function prior to, during, and after therapy. Use of telavancin in patients with pre-existing moderate/severe renal impairment ($CrCl \leq 50$ mL/min) should be considered only when the anticipated benefit outweighs the potential risk. In regard to safety during pregnancy, adverse developmental outcomes have been observed in animal studies. Prior to use, women of childbearing potential should have a serum pregnancy test. Telavancin is not recommended during pregnancy unless the potential benefit outweighs the risk to the fetus. Common adverse effects include diarrhea, taste disturbance, nausea, vomiting, headache, and foamy urine.⁹⁷

NEW INDICATIONS FOR QUINOLONES

The FDA added further indications for two newer generation fluoroquinolone class antimicrobials. In April 2001, *moxifloxacin*, and in October 2002, *gatifloxacin*, were FDA approved for use in uncomplicated skin and skin structure infections. Several studies supported these new indications. In one multicenter trial involving 410 patients with uncomplicated skin and soft tissue infections, a once daily gatifloxacin dose of 400 mg orally had a cure rate of 91%.⁹⁸ This compared to the control group, which received a once daily oral dose of 500 mg of levofloxacin and had a cure rate of 84%. Another study examined the efficacy of moxifloxacin versus cephalexin in patients with uncomplicated skin infections.⁹⁹ The clinical effectiveness was 90% for the group receiving oral moxifloxacin (400 mg once daily) and 91% for the group receiving oral cephalexin (500 mg three times daily). Both groups received the antimicrobials for a total of 7 days. Other studies have also supported these findings.¹⁰⁰

In April 2003, gemifloxacin was approved for the treatment of community-acquired pneumonia and acute exacerbations of chronic bronchitis. It is a dual targeted fluoroquinolone with potent in vitro activity against gram-positive, gram-negative, and atypical human pathogens that are key causes of community-acquired respiratory tract infections.¹⁰¹ Gemifloxacin has also been shown to be efficacious in gram-positive skin and soft tissue infections. It was studied in rat models with wound infections caused by *S. aureus*, *S. epidermidis*, and *S. pyogenes*. Compared to ciprofloxacin, grepafloxacin, trovafloxacin, tosufloxacin, amoxicillin-clavulanate, cefuroxime, and azithromycin, gemifloxacin demonstrated the greatest reduction in mean bacterial numbers. No comparator agent had greater activity than gemifloxacin against *S. aureus* or *S. pyogenes*.¹⁰²

NEW ANTIFUNGAL AGENTS (TABLE 3.2)

The increasing burden of invasive fungal infections (IFIs), especially among hospitalized patients with immune

Table 3.2 Novel Antifungal Agents for Invasive Fungal Infections

Generic name	Brand name	Mechanism of action	Dosage	Indications
Voriconazole	Vfend	Interfere with fungal cell wall synthesis by inhibiting 14 α -demethylase synthesis of ergosterol	200 mg BID PO or 3–6 mg/kg BID IV for 14 days after resolution of symptoms	Candida, IFIs, drug of choice for aspergillus
Posaconazole	Noxafil		200–400 mg BID PO	Candida, IFIs
Anidulafungin	Eraxis	Interferes with fungal cell wall synthesis by inhibiting 1,3-beta glucan synthase synthesis of 1-3-beta glucan	50–100 mg IV q 24 hours for 14 days after symptom resolution	Candidemia/candidiasis

compromise, has created an urgent need for novel antifungal therapies. The two major causes of invasive fungal infection are *Candida albicans* and *Aspergillus fumigatus*, although other emerging fungi, such as non-*albicans* *Candida* (particularly *Candida glabrata*), *Fusarium*, and Zygomycetes, are contributing to the need to expand our armamentarium of antifungal agents.¹⁰³

Voriconazole and Posaconazole

Voriconazole and posaconazole are new triazole agents with broad-spectrum activity against many fungi. As with all azole antifungal agents, voriconazole and posaconazole work by interfering with synthesis of the fungal cell wall element, ergosterol, through inhibition of cytochrome P450 14 α -demethylase.¹⁰⁴ Voriconazole was FDA approved in 2002 for primary treatment of acute invasive aspergillosis and salvage therapy for rare but serious fungal infections caused by the pathogens *Scedosporium apiospermum* and *Fusarium* spp. Voriconazole also demonstrates superior activity in vitro against fluconazole-resistant *C. glabrata* and against *C. krusei*.

- Posaconazole was approved in 2006 and is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, with immune compromise as well as for the treatment of oropharyngeal candidiasis, refractory to itraconazole and/or fluconazole.¹⁰⁵

Voriconazole has become the drug of choice for treatment of invasive aspergillosis. In a study comparing voriconazole to amphotericin B in 277 patients with proven or probable aspergillosis, voriconazole led to better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B.¹⁰⁶ Voriconazole may be administered both orally and intravenously. In clinical trials, oral (200 mg twice daily) and IV (3–6 mg/kg every 12 h) doses have produced favorable response.¹⁰⁷ Side effects include dose-related, transient visual disturbances, skin rash, elevated hepatic enzyme levels, and periostitis.¹⁰⁷

Two randomized multicenter trials have assessed the efficacy of posaconazole (200 mg PO tid) in preventing IFIs compared to standard azole therapy (fluconazole or itraconazole) in high-risk patients with neutropenia or graft versus host disease. A prospective nonblinded study in high-risk neutropenic patients with neutropenia due to either AML or MDS randomized 602 patients to receive posaconazole ($n = 298$) or either fluconazole or itraconazole ($n = 304$) until neutrophil recovery or occurrence of an invasive fungal infection for up to 84 days.¹⁰⁸ Proven or probable infections were diagnosed in seven patients (2%) in the posaconazole group versus 25 (8%) in the comparator group. The majority of breakthrough infections in the fluconazole/itraconazole arm were due to aspergillosis.

A double-blinded study in allogeneic hematopoietic stem cell transplant patients with graft versus host disease (GVHD) compared fluconazole ($n = 299$) or posaconazole ($n = 301$) for up to 112 days or until the occurrence of an invasive fungal infection. Proven or probable infections were diagnosed in 16 patients (5%) in the posaconazole group and 27 (9%) in the fluconazole group.¹⁰⁹

An open-label, multicenter, case-controlled clinical trial of posaconazole as salvage therapy in patients with IFIs has also been completed for a variety of IFI that failed primary therapy (predominantly amphotericin B regimens). Among patients with aspergillosis ($n = 107$), the global response to

posaconazole therapy (800 mg/day divided doses) was 42% versus 26% response in contemporary control patients who received other licensed antifungal therapy ($P = 0.006$).¹¹⁰

Preliminary data have also suggested that posaconazole may be an effective therapy for zygomycosis unresponsive to amphotericin B-based regimens.¹¹¹

Posaconazole was initially only available as an oral suspension, which required intake with high-fat meals for absorption, limiting its utility in the critically ill patient. The major adverse effects appear to be gastrointestinal, including diarrhea, nausea and vomiting, and rashes.^{108,112} In 2013, the FDA approved delayed-release tablets for prophylaxis of invasive *Aspergillus* and *Candida* infections in high-risk patients, such as those with hematologic malignancies with prolonged chemotherapy-induced neutropenia and hematopoietic cell transplant recipients with GVHD. Administration with food is recommended, because it demonstrates less pharmacokinetic variability when given with food. In 2014, the FDA approved an IV for prophylaxis of invasive *Aspergillus* and *Candida* infections in high-risk patients aged 18 years and older.¹¹³ This is useful for patients when oral administration is not a viable option or in cases in which absorption may be of concern.¹¹³

Anidulafungin

Anidulafungin is a novel echinocandin approved in 2006 for the treatment of candidemia as well as for candidal esophagitis, abdominal abscesses, and peritonitis.¹¹⁴ As with other echinocandins, anidulafungin blocks the synthesis of a major fungal cell wall component, 1,3-beta glucan, presumably via inhibition of 1,3-beta-glucan synthase.¹¹⁵

In a multicenter, randomized, blinded trial that compared anidulafungin with fluconazole in the treatment of invasive candidiasis, treatment was successful in 75.6% of patients treated with anidulafungin, as compared with 60.2% of those treated with fluconazole ($P = .01$).¹¹⁶

Another randomized, double-blind, double-dummy study compared the efficacy and safety of IV anidulafungin to that of oral fluconazole in 601 patients with esophageal candidiasis and found it to be statistically noninferior¹¹⁷; nonetheless, fluconazole is still the first choice treatment due to lower cost. The majority of patients with esophageal endocarditis are AIDS patients who live in poor areas of the world. Anidulafungin can be used as an alternative therapy to fluconazole for patients who have poor tolerance to fluconazole or for esophageal candidiasis due to fluconazole-resistant *Candida*.¹¹⁸

Anidulafungin is available as an IV infusion. Dosing for esophageal candidiasis is 100 mg on day 1, then 50 mg/day. Dosing for candidemia is 200 mg on day 1, then 100 mg/day. Similar to other echinocandins, anidulafungin is well tolerated. In clinical trials the most common side effects (<5%) are abnormal LFTs.¹¹⁷ Infusion-related reactions can occur when the infusion rate exceeds 1.1 mg/min. Elimination occurs through nonenzymatic reactions and degradation through bile. It is the least likely of the echinocandins to cause a drug reaction, because it is not a substrate, inhibitor, or inducer of CYP450 enzymes.

NEW DOSING OF ANTIVIRALS (TABLE 3.3)

Famciclovir

A study in 701 patients with herpes labialis demonstrated that famciclovir 1500 mg single-dose therapy was as efficacious as

Table 3.3 Novel Dosing of Antivirals for Herpes Labialis

Agent	Dosing
Famciclovir	1500 mg single dose
Valacyclovir	2000 mg BID for 1 day

750 mg twice daily for 1 day and reduced the time to healing of lesions by 2 days when taken within 2 hours of onset of prodromal symptoms.¹¹⁹

Valacyclovir

Two multicenter, randomized, double-blind, and placebo-controlled studies in 1524 and 1627 patients with herpes labialis demonstrated that high-dose therapy with valacyclovir (2000 mg twice daily for 1 day) shortened the healing time of lesions by 1 day compared with placebo and that a second day of therapy provided no additional benefit.¹²⁰ Therapy should be started at the earliest sign of a cold sore (such as tingling, burning, or itching).

A NEW TYPE OF ANTIMICROBIAL (NOT FDA APPROVED)

Teixobactin is the newest antimicrobial that was discovered in a screen of uncultured bacteria using a technology called iChip. Soil is diluted with nutrient agar and placed into the iChip. The surface is covered with tiny wells separated by semipermeable membranes that can trap individual bacteria cells. Extracts from 10,000 isolates were screened for antimicrobial activity to plates containing *S. aureus*. One such extract from *Eleftheria terrae* was shown to have good activity. The researchers isolated a unique compound; a depsipeptide that contains enduracidine, methylphenylalanine, and four D-amino acids. This came to be known as teixobactin.

The mechanism of action is inhibition of cell wall synthesis by binding to a highly conserved motif of lipid II (precursor of peptidoglycan) and lipid III (precursor of cell wall teichoic acid). It has excellent activity against gram-positive pathogens, including those strains that are drug resistant. It demonstrated efficacy against enterococci, *M. tuberculosis*, *C. difficile*, and *B. anthracis*. It is bactericidal against VISA. It was also found to be effective in vivo, when used to treat mice infected with MRSA and *S. pneumoniae*. It has not been shown to be efficacious against gram-negative organisms. They were not able to obtain any mutants of *S. aureus* or *M. tuberculosis* that were resistant to teixobactin, likely due to its unique mechanism of action.

Although teixobactin is a promising new therapy to treat MRSA infections, this antibiotic is very early in its inception. Further testing is needed to determine if this antibiotic will be safe and effective in humans.¹²¹

CONCLUSIONS

Skin and soft tissue infections are commonly encountered in the ER setting. As MRSA infection becomes more prevalent and other resistant organisms continue to emerge, it is essential for physicians to be aware of newly approved antimicrobials, their indications for use, dosing, and side effect profiles. To maintain an armamentarium of useful agents, antimicrobials should be utilized only when necessary and in the context of local resistance patterns.

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Use of biologic agents in cutaneous emergencies

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Biologic agents are proteins or antibodies engineered to target specific molecules. They are derived from the products of living organisms. In recent years, numerous drugs of this type have been added to the therapeutic armamentarium in various disciplines of medicine. In dermatology, psoriasis and chronic urticaria are so far the only entities for which some of these drugs have been approved. They include the tumor necrosis factor- α (TNF- α) blockers like infliximab, etanercept, and adalimumab; inhibitors of proinflammatory cytokines (IL12, IL17, IL23, IL27) like ustekinumab and secukinumab, and other monoclonal antibodies such as anti-IgE (omalizumab) and anti-CD 20 (rituximab). New agents are currently under development undergoing different stages of clinical investigation.

Biologic drugs have been used off-label in numerous skin diseases, some of which are dermatologic emergencies. Treatment reports and case series are more numerous with the TNF blockers group, but increasing development of new biologic agents is opening additional alternatives for possible indications in many other skin diseases.

INFLIXIMAB

Infliximab (Remicade; Centocor, Inc., Horsham, Pennsylvania) is a chimeric mouse/human monoclonal antibody (IgG1) that binds and inhibits both soluble and transmembrane TNF- α . It contains a variable murine region and a constant human IgG1 region including Fc constant region. It activates lysis of cells that express transmembrane TNF- α via antibody-dependent and complement-dependent cytotoxic mechanisms.¹

Indications

Infliximab is approved for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis, Crohn disease (adult and pediatric), ulcerative colitis (adult and pediatric), and severe plaque-type psoriasis.²

Dosage

Infliximab is administered as an intravenous (IV) 3–5 mg/kg (in most diseases) infusion, at initiation, week 2, week 6, and subsequently every 8 weeks. It is also sometimes administered as a 300 mg infusion.^{1,2}

Side Effects

Most of the side effects that have been described correspond to infusion reactions, which occur in approximately 10%–20% of patients and tend not to be serious. These include headache, dyspnea, hypotension, and dermatitis among others.^{3,4}

Part of the infliximab molecule is murine in origin; hence, the development of neutralizing antibodies has been described

in between 15% and 50% of cases, depending on the study. The presence of neutralizing antibodies is associated with low plasma levels of infliximab, high titers of TNF- α , an increased risk of adverse events (especially infusion reactions), and increase of disease activity. The concomitant use of immunosuppressant drugs, such as cyclosporine or methotrexate, has been shown to reduce the rate of formation of neutralizing antibodies.⁵ The development of antinuclear antibodies (ANAs) has also been reported in 20%–75% of patients receiving infliximab; however, this finding does not affect the efficacy of the drug.^{6,7}

Postmarketing data from infliximab-treated patients with RA, Crohn disease, or other indications for which infliximab is approved suggest a potential increased risk for tuberculosis, which can also present as disseminated or atypical disease, invasive fungal infections, other infections due to opportunistic pathogens, blood cell abnormalities, lymphoma, demyelinating disease, and congestive heart failure, mostly in patients with a clinical history of heart disease.²

ETANERCEPT

Etanercept (Enbrel; Amgen and Wyeth, Thousand Oaks, California) is a recombinant fusion protein comprising domains of the 75-kDa human TNF receptor, linked to the Fc portion of human IgG 1, which inhibits the activity of TNF- α . It binds to soluble and membrane bound TNF. Binding of etanercept prevents TNF from binding to its receptor, thereby effectively blocking its physiologic functions. Unlike infliximab, it does not fix complement, cause antibody-dependent cytotoxicity, or trigger T-cell apoptosis.^{1,3}

Indications

Etanercept is approved for use in moderate-to-severe RA, polyarticular-course juvenile RA, ankylosing spondylitis, psoriatic arthritis, and chronic moderate-to-severe plaque psoriasis.⁸

Dosage

Recommended dosage for RA, ankylosing spondylitis, and psoriatic arthritis is 25 mg administered subcutaneously twice weekly for the entire year. For plaque-type psoriasis patients, the dosing is 50 mg twice weekly for the first 12 weeks followed by a “step-down” to 25 mg twice weekly for another 12 weeks or 25 mg twice weekly for 24 weeks.⁸

Side Effects

Injection site reactions may occur in up to 40% of patients. The rate of development of anti-etanercept antibodies has been less than 10% and has not been observed to lead to decreased efficacy.⁹

Long-term data from clinical trials in many patients receiving etanercept for other indications, such as RA, found infrequent cases of tuberculosis as well as other infectious complications, a possible increased risk of certain neurologic demyelinating disorders, rare cases of pancytopenia, and increased risk of hematologic malignancies and congestive heart failure. A surveillance study for psoriasis patients under etanercept treatment did not show increased frequency of serious adverse events compared to control groups.^{9,10}

RITUXIMAB

Rituximab (Rituxan; Genentech, South San Francisco, California) is a chimeric murine-human monoclonal antibody to CD20, which induces depletion of B cells in vivo. In 1997, rituximab became the first monoclonal antibody approved for treatment of malignancy.¹ Rituximab binds to cell surface CD20, inducing cytotoxicity by several mechanisms, including cell-dependent cytotoxicity, complement-mediated lysis, and direct disruption of signaling pathways and triggering of apoptosis. Apart from depleting CD20+ B-cell population, it downregulates T-cell autoreactive clones by inhibiting B-cell antigen-presenting signals. Rituximab results in depletion of normal as well as malignant B cells, leading to investigation of its use in autoimmune disorders, including autoimmune blistering disorders, systemic lupus erythematosus (SLE), RA, autoimmune thrombocytopenia and hemolytic anemia, anti-neutrophil cytoplasmic antibody-positive vasculitis, and autoimmune neuropathies.^{10–12}

Indications

Rituximab is indicated for use in non-Hodgkin lymphoma (NHL), relapsed or refractory, low grade or follicular CD20+ B-cell lymphoma; and active RA in combination with methotrexate, not responsive to one or more TNF antagonist therapies. It is also currently approved for the treatment of Wegener granulomatosis and microscopic polyangiitis in combination with glucocorticoids.¹³

Dosage

There are two main dose regimens. For NHL, 375 mg/m² in four weekly infusions is administered while two 1000 mg IV infusions separated by 2 weeks is used for RA.¹³ Both have been tried for such dermatologic conditions as blistering diseases.

Side Effects

CD20 is a B cell-specific antigen expressed on the surface of B lymphocytes throughout differentiation from the pre-B cell to the mature B-cell stage but not on plasma cells or stem cells. Because plasma cells and hematopoietic precursors are spared, immunoglobulin levels do not fall dramatically; humoral immunity against common pathogens is relatively spared; and B cells typically begin to return to the circulation within 6 months of therapy. The incidence of serious adverse effects with rituximab is relatively low. Infusion reactions are the most common adverse effects. In most cases, these are mild and occur only with the first infusion. In a study of rituximab for the treatment of RA, infections occurred in 35% of patients in the rituximab group compared with 28% of the placebo group. Serious infections occurred in 2% of the rituximab group compared with 1% of the placebo group. Rituximab is not recommended for

patients with HBV infection, because it can cause reactivation of the disease.¹⁴

OMALIZUMAB

Omalizumab (Xolair; Novartis, Basel, Switzerland) is a recombinant DNA-derived humanized IgG1 monoclonal antibody that selectively binds to free and membrane-bound IgE antibodies. It binds to free IgE in the circulation, not to receptor-bound IgE, and prevents cross-linking of IgE bound to its high affinity receptor.¹⁵

Indications

Omalizumab is indicated for the treatment of moderate to severe persistent asthma in patients older than 12 years of age and chronic idiopathic urticaria in patients unresponsive to H1 antihistamine treatment.¹⁶

Dosage

Omalizumab is administered subcutaneously for asthma at 150 or 300 mg every 2 weeks and for chronic idiopathic urticaria at 150–300 mg every 4 weeks.¹⁶

Side Effects

The most common adverse events include injection site reactions, headache, arthralgia, nausea, fatigue, and dizziness. Hypersensitivity reactions and anaphylaxis are rare but may occur.^{15–17}

BLISTERING DISEASES

Pemphigus

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are autoimmune blistering disorders of the skin and mucous membranes that are characterized by autoantibodies directed against desmoglein (DSG) 3 and DSG 1, respectively. These may be life-threatening diseases requiring urgent therapy with high-dose systemic corticosteroids and immunosuppressive therapy for long periods of time. This carries high risks for potential complications, such as severe infections.^{18,19} TNF levels have been found to be increased in lesional skin and sera of patients with PV.²⁰ IL 1 α , IL 10, TNF α , and TGF β were measured in sera of 25 patients with PV and 25 normal controls. All cytokines were increased in PV patients except IL10, which was increased but the difference did not reach statistical significance.²¹ Antiinterleukin-1 α (IL-1 α) and anti-TNF- α antibodies reduce the acantholytic detachment and keratinocytes exposed in vitro to PV IgG synthesize IL-1 α and TNF- α .²²

Two cases have been described of recalcitrant PV refractory to multiple immunosuppressant treatments but rapidly responsive to treatment with infliximab. In both cases, the patients showed a lasting response (4 months and 104 weeks, respectively).^{23,24}

In a multicenter trial of patients with PV, 20 patients were randomized to prednisone alone or prednisone and infliximab. The results showed acceptable safety margins for the infliximab/prednisone group with no serious adverse effects registered and no increase in infectious complications, compared to the prednisone alone group. The efficacy of both treatments did not show statistically significant differences, but a

favorable tendency toward the infliximab arm was observed. Measurements of anti-DSG 1 and 3 were significantly lower for the infliximab group.²⁵

In another study, five patients with PV, nonresponsive to prednisone and concomitant immunosuppressive therapy, were treated with etanercept 25 mg twice weekly and methotrexate 12.5 mg weekly for 16 weeks (one patient required 20 mg). At the end of the treatment, prednisone had been tapered to <20 mg/daily, and methotrexate was used as maintenance therapy. The follow-up period was 24 ± 6 months.²⁶ Another group reported six cases treated with etanercept with an overall response rate of 50%. The study was interrupted due to recruitment failure.²⁷

For the last 10 years, there have been extensive studies about treatment of pemphigus vulgaris with rituximab. Rituximab is capable of depleting normal and pathogenic CD20+ B-cell population, which is expressed throughout most of the B-cell lineage, from the late pro-B cell to the memory B cell, thus suppressing pathogenic autoantibody production and sparing long-lived plasma cells. This may account for the main mechanism by which rituximab is highly effective in controlling refractory pemphigus and producing a rapid response. The antibody remains in the plasma membrane, contributing to its persistent effect. B-cell reappearance shows a naïve phenotype like in neonatal cord blood (CD19+ CD27-); thus rituximab appears to reset the B-cell population.^{1,28} Relapses are frequent, however, and may arise in persisting memory cells in the spleen and lymph nodes, novel lineages of autoreactive B cells, long-lived autoreactive plasma cells, and/or autoantibodies against rituximab.¹²

There is no established consensus about the dose of rituximab for pemphigus. Both lymphoma and RA protocols have been used. A recent review of different dosing schemes did not show a beneficial tendency toward any of them and supports the fact that low dose cycles (<1500 mg/cycle) can also control the disease, though in this case, shorter duration of complete remission (CR) was observed.²⁹ As to the frequency of the infusions there are authors in favor of treating with a fixed protocol for at least 4 months independent of disease remission and others who advocate the administration of rituximab be concordant with relapses after CR.³⁰

Five prospective trials have proven the efficacy of rituximab for the treatment of pemphigus.^{31–35} In 2007, 21 patients with PV and PF received one cycle of rituximab. They were steroid-resistant or dependent or had contraindications to receive corticosteroids. The patients received four weekly infusions of 375 mg/m² of rituximab. CR was observed in 86% of the patients. At 3 weeks of therapy, peripheral B cells were decreased by 99%, with a significant decrease in anti-DSG 1 and 3 antibodies. Persistent high titers were observed in patients who had delayed complete remission. B cells returned to normal at 6 months, expressing naïve phenotype (CD19+ CD27-). Serum IgG levels and antibodies against pneumococcal capsule polysaccharide and tetanus toxin did not vary. With a mean follow-up period of 12 months, 50% of the patients required additional therapy.³² Two patients had severe infections with one dying, despite normal Ig levels. These results are comparable to other trials and case series.

In a more recent study of 40 PV unresponsive patients treated with rituximab, 22.5% of the patients experienced severe infectious complications, such as disseminated herpes simplex, lung abscess, skin abscess, pneumonia, and sepsis. Concomitant immunosuppressive therapy was also being administered.³⁵

A comprehensive analysis on the use of rituximab for PV was published in 2014.³⁶ Approximately 500 patients were treated, most of them according to the lymphoma protocol. The majority of the patients received additional immunosuppressive therapy before and after rituximab. The following observations were noted: (1) clinical remission on therapy was observed in 90%–95% of the cases in less than 6 weeks; (2) CR was achieved at 3 or 4 months; (3) a small percentage of patients did not need further therapy and maintained sustained remission; (4) the incidence of relapse was at least 50%, and 60%–90% of the patients required further treatment cycles; and (5) the majority of patients in CR were still on immunosuppressive therapy. Rituximab is one of the best biologic agents for the treatment of PV; overall, serious adverse events are seen between 2% and 5% of the patients, and close monitoring for infectious complications is highly recommended.

There have been case series with patients diagnosed with PF, and the same tendency is observed. The largest case accounts for 12 patients with refractory disease for 4 years. Six patients achieved CR and four partial remission (PR) with anti-DSG 1 antibodies correlating with disease activity.³⁷

The combination of rituximab and IVIG seems especially useful, as there may be synergic effects between these two agents. While rituximab depletes the whole B-cell antibody-producing pool with consequent immunosuppression, IVIG rapidly decreases pathogenic antibodies and provides protecting defenses against infections.³⁸

Eleven refractory PV patients were treated with two cycles of rituximab at 375 mg/m², once weekly for 3 weeks and one cycle of 2 gr/kg of IVIG the fourth week. They maintained consolidation therapy once a month during 4 months. Nine patients achieved complete and sustained remission; two patients relapsed and received extra cycles of rituximab until they reached CR.³¹ A second stage of this protocol was published in 2015 reporting long-term follow-up of 10 years of 10 of 11 of these patients with excellent outcome, no relapses, no deaths, and no adverse events after discontinuation of rituximab.³⁹ The same authors recently published a retrospective analysis of 10 patients with PV with contraindications to conventional therapy, who had received rituximab and IVIG as first-line therapy. The patients were treated with the lymphoma protocol for two cycles and then with consolidation therapy for 4 months. IVIG was administered (2 gr/kg/cycle) with B cells being absent, until they returned to normal. Infusions were continued according to the protocol. CR was obtained in 100% of the patients, with no adverse events and no relapses.⁴⁰

Veltuzumab, a second-generation humanized monoclonal anti-CD20 antibody, has been tried in a patient refractory to rituximab. The patient had CR off therapy and required additional veltuzumab therapy to control a relapse at 24 months. It is administered subcutaneously, which is an important advance over rituximab.^{12,41}

Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is a heterogeneous group of autoimmune subepithelial blistering disorders that primarily affect mucosal surfaces and, occasionally, the skin. MMP was previously called benign mucous pemphigoid; the outcome might not always be benign. Due to its scarring nature, there is a group of high-risk patients who require prompt therapy preventing possible blindness, deafness, or strictures of

the pharynx, esophagus, larynx, and/or anogenital mucosa. Conventional immunosuppressive therapy is used in these cases with high-dose methylprednisolone, cyclophosphamide, methotrexate or mophetil mycophenolate. Autoantibodies to β -4-integrin, α -6-integrin, bullous pemphigoid (BP) antigen (Ag) 1, BP Ag 2, and laminin 5 have been detected. IgG, IgA, and C3 deposits are found along the basement membrane zone. Consecutive cycles of inflammation and scarring of mucosal surfaces are observed in this disease.^{42,43} Patients with ocular CP have elevated levels of serum TNF- α compared with normal controls,⁴⁴ and it has been demonstrated that TNF is also elevated in conjunctiva of CP patients and induces profibrotic changes in conjunctival fibroblasts.⁴⁵ This appears to be the reason why several cases of recalcitrant scarring CP refractory to conventional immunosuppressive therapy responded to anti-TNF agents.

Only one case of MMP treated with infliximab has been described. The process was highly aggressive and refractory to multiple immunosuppressant treatments, and infliximab at standard dose, and regimen led to remission of the disease in the oral and pharyngeal mucosa and stabilized the ocular involvement, which had led to the loss of an eye.⁴⁶

Etanercept appears to be particularly useful in these patients, and since 2002, when the first case was reported,⁴⁷ seven other cases showed promising results.^{48–52} The patients presented ocular and/or oropharyngeal disease and were generally refractory to treatment with methylprednisolone, cyclophosphamide, azathioprine, or methotrexate, among others, and disease progression was fast with severe sequelae. In most cases, etanercept at a 25 mg dose twice a week stopped disease progression and improved outcome with regression of scarring lesions as well in one case.

Being an autoantibody mediated disease, rituximab proved to be useful in the management of these patients. Due to its B-cell depletion effect, it inhibits antibody production with considerable reduction in autoantibodies, and it also suppresses B cell-mediated antigen presentation to T cells, which play a pivotal role in the propagation of cell-mediated autoimmune response.⁵³ In 2007, the first case of recalcitrant MMP treated with rituximab infusions was reported,⁵⁴ after which numerous cases and case series appeared. Due to the rarity of the disease, prospective controlled trials have not been done.⁵⁵ A retrospective series of 49 patients has since been published.⁵⁶ All patients had the diagnosis of MMP. Twenty-four patients were treated with rituximab + conventional immunosuppressive therapy, and 25 patients received conventional therapy alone. In the rituximab group, 100% of the patients achieved disease control compared to 40% in the conventional therapy alone group. Relapse rate was 42% and 33%, respectively, and maintenance of immunosuppressive therapy was needed to establish disease remission. Adverse effects were comparable in both groups with no serious events reported for rituximab. The results of this study are comparable to previous retrospective series with high rates of complete response, but a relatively short remission period with frequent relapses, probably attributed to normal B-cell population return. It was also noted that ocular disease responded better than laryngeal, and the drug does not appear to affect the scarring process. In a case series of six ocular MMP patients treated with rituximab,⁵⁷ all patients achieved CR, and further conjunctival scarring and blindness were prevented. Relapses occurred in the majority of patients, and further treatment cycles were administrated.

Bullous Pemphigoid

BP is a subepidermal autoimmune blistering disorder, characterized by autoantibodies against BP Ag 1 and 2. BP is usually considered a benign bullous disease, particularly compared with PV; yet, it can be lethal, especially in elderly patients or in those in need of higher steroid doses. In BP, TNF levels are elevated in both serum, and blister fluid and correlate with the severity of disease.^{58,59} TNF- α is thought to mediate the recruitment of neutrophils, and eosinophils seen in the inflammatory infiltrate of BP lesions and stimulate the production of other inflammatory cytokines and chemokines. There have been four cases of BP treated with etanercept: all patients had concomitant psoriasis or psoriatic arthritis, and one patient was treated with rituximab as well. Etanercept appears to be a reasonable choice for patients with both diseases.^{60–63}

Rituximab appears to be a very effective agent in controlling bullous pemphigoid. Several case reports and retrospective series reflect a high percentage of patients with complete responses after the first or second cycle.⁶⁴ Both lymphoma and RA dosing protocols were applied, but the latter is more widely used. A very interesting study showed significant reduction in IgG anti-BP180 in BP patients after the first rituximab infusion with no change in IgG anti-varicella zoster virus and an increase in B-cell activating factor. This favors the theory that the drug decreases B cells, precursors to short-lived plasma cells that produce autoantibodies, but does not affect long-lived plasma cells that produce nonpathogenic antibodies.^{65,66}

A critical analysis of the current literature reviewed 16 patients treated with rituximab, 11 achieved CR, 1 PR, and 1 was a nonresponder (NR). Three patients died, two from infectious complications, but they were on immunosuppressive therapy as well, and one from cardiac arrest 10 days after rituximab infusion. The mean follow-up period was 15.6 months.⁶⁷ Another retrospective series⁶⁸ compares one group of 13 patients who received rituximab (4 infusions \times 500 mg/weekly) plus prednisone as first-line therapy (R group) versus 19 patients who received only prednisone (C group). CR was observed in 92% of the patients in R group versus 53% of the patients in C group ($P = .02$). Of the patients in R group, 31% versus 53% of the patients in P group had infectious complications, and 1-year mortality was 15% and 37%, respectively. These differences were not statistically significant. Both authors agreed that rituximab is a promising agent as first-line therapy in high-risk patients requiring systemic therapy and that infectious complications are the main concern.

Another study described a novel protocol to treat bullous pemphigoid refractory patients with the combination of IVIG and rituximab.⁶⁹ The patients were given one cycle of 2 gr/kg of IVIG at the beginning followed by eight weekly infusions of 375 mg/m² of rituximab followed by four equal monthly infusions and then continued with monthly infusion of IVIG until the B-cell population was restored. All the patients achieved complete remission, with no adverse events and no deaths with a follow-up period of 6 years. This combination advocates the same principle as in PV.

There have been some studies of the role of IgE and eosinophils in BP. IgE appears to be elevated in most BP patients, and IgE antibodies against BP antigens have been found in 90% of the patients.⁷⁰ Besides, the early phase of the disease resembles urticaria. This led to the therapeutic use of omalizumab for refractory cases of BP. Up to date, 10 cases of refractory BP have been treated with omalizumab according to the asthma protocol (300 mg every 2 weeks). All but one patient had a positive

response with clearing of the lesions and significant decrease in pruritus.^{15,71} Future studies will be necessary to assess the real efficacy of this promising agent.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) usually presents with painful mucosal ulcerations and polymorphous skin lesions, which usually progress to blistering eruptions on the trunk and extremities. A wide variety of both benign and malignant tumors are found in these patients, especially hematologic malignancies. Most reported patients die from their underlying tumors, whereas others may die from bronchiolitis obliterans. The mortality rate has been reported to be as high as 90%. Initial conventional immunosuppressive therapy is classically administered though refractory cases are common.⁷² Before 2005, there were five reported cases of PNP treated with rituximab. Three case reports described significant improvement in oral and cutaneous lesions after rituximab, and two reports describe less successful responses, especially with regard to mucosal lesions.⁷³ Rituximab is especially helpful in patients with associated follicular NHL in which response may be of dual origin due to remission of malignancy. A review of 13 patients with CD20+ malignancy and PNP and found that only two patients had progression of disease despite therapy.⁷⁴ It has also been observed that advanced neoplasms with PNP have a poorer response, and bronchiolitis obliterans does not improve in spite of rituximab administration and represents the main cause of death in these patients.^{72,75-77}

ACUTE GRAFT VERSUS HOST DISEASE

Acute GVHD results from donors' immune cells recognition of the host's tissues as foreign. The skin, gastrointestinal tract, and liver represent the principal affected organs. Clinically, it manifests with dermatitis, elevated bilirubin, nausea, vomiting, and diarrhea. The main therapeutic agents used to control the disease are systemic corticosteroids and immunosuppressive agents.⁷⁸

Less than 50% of patients with GVHD will respond to first-line therapy with high-dose systemic corticosteroids. Acute GVHD is the main cause of morbidity and the most important cause of relapse-unrelated death after allogeneic bone marrow transplantation. When first-line therapies fail, steroid-resistant GVHD overcomes, worsening prognosis with a mortality rate of 70%. To date, no treatment has been found to improve resistant disease prognosis, and in that matter prophylaxis regimens are very important.⁷⁹

TNF- α is implicated in GVHD pathophysiology, as it is released along with other proinflammatory cytokines, both during the conditioning pretransplant period and after antigen-presenting cells are stimulated.⁸⁰ In this setting, infliximab has proven to be an interesting therapeutic choice, alone or in combination with steroids or other biologic agents, especially against steroid-refractory GVHD.

There have been several case reports and case series to assess the efficacy of this treatment as well as the incidence of adverse events, especially infliximab-related infections. Infliximab has been reported to increase invasive fungal infections. The dose varies from 10 mg/kg administered once a week up to four times a week.

Infliximab failed to improve GVHD prophylaxis and presented higher risk of infections in a study involving 19 patients.⁸¹

In a phase III trial comparing two regimens (infliximab + corticosteroids versus corticosteroids alone) for the initial treatment of acute GVHD in 63 patients, no significant differences were found in response or adverse events between the two groups. In both groups half of the patients required salvage treatment with another agent for lack of response.⁸²

In steroid-refractory GVHD, recent case series tend to show promising initial responses with infliximab, especially patients with gastrointestinal compromise, either as single agent or combined with other biologic agents. A high number of patients achieved complete or partial responses, but short-term follow-up showed a high mortality rate, mainly due to infections or progressive GVHD.⁸³⁻⁸⁵

In a study of 21 patients, who had received infliximab and basiliximab for the treatment of acute gastrointestinal GVHD, only five patients were nonresponders, but the survival rate at 1 year was 24% with disease progression or malignancy relapse being the main causes of death.⁸⁶

In another report, of 17 patients treated with infliximab and daclizumab, 47% achieved partial or complete response, but all patients died at a median of 6.7 months. Pediatric populations tend to show equal results.⁸⁷

Anti-TNF- α infliximab may have significant activity as a second- or third-line therapy for acute GVHD, but it fails to improve survival rates that remain very poor for steroid-refractory patients.

Etanercept has shown promise in the treatment of acute GVHD. It was evaluated in 13 patients with refractory GVHD showing an overall response of 62%, with four patients achieving CR, two PR, and four deaths (two from GVHD progression, one from disease progression, and one from invasive fungal infection).⁸⁸

In a phase II study of etanercept in combination with the interleukin-2 receptor antibody daclizumab for the treatment of steroid-refractory acute GVHD in 21 patients, the overall response rate was 67% (38% CR, 29% PR).⁸⁹ Similarly, in a pilot study on the use of etanercept in combination with tacrolimus and methylprednisolone as initial therapy for 20 patients with stage II or III acute GVHD, 75% of patients had a complete response within 4 weeks of initiating treatment.⁹⁰

A prospective study compared 61 patients with new-onset GVHD treated with methylprednisolone and etanercept as initial therapy versus 99 patients treated with corticosteroids alone. CR was achieved by 69% versus 33% of the patients by week 4. TNF receptor 1 levels, a biomarker for GVHD activity, were measured, and all patients in CR had a significant decrease. This could lead to further investigations using etanercept along with corticosteroids as first-line therapy, possibly decreasing steroid-refractory cases.⁹¹

STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute, life-threatening mucocutaneous diseases characterized by widespread sloughing of the epidermis and of the mucous membranes. Mortality is high and increases with more extensive skin detachment.⁹²

With a drug or its metabolite acting as a triggering antigen, pathogenesis of TEN involves a cascade of immunological events resulting in keratinocyte death. This is principally T-cell mediated by CD8+ lymphocytes and also NK cells. Keratinocyte apoptosis is then triggered by different mediators

that include granulysin, perforin/granzyme B, Fas and FasL, nitric oxide (NO), and TNF- α .^{92,93}

The role of TNF- α in TEN has not been completely elucidated. TNF was elevated in serum, blister fluid, and skin samples from TEN patients. It also has been demonstrated that a strong population of CD40 ligand expressing T cells was found in SJS/TEN patients. The CD40/CD40 ligand system stimulates the secretion of TNF- α , NO, IL-8, and other adhesion molecules.^{92,94} TNF- α and INF- γ , both secreted by activated T cells, are implicated in drug-stimulated immune response and enhance apoptotic mediators.⁹⁵ TNF- α induces apoptosis by joining TNF-R1 (death receptor) which starts caspase activation, and stimulates nitric oxide synthetase. NO-dependent FasL upregulation with subsequent keratinocyte apoptosis increases. Moreover, NO and TNF also enhance reactive oxygen species and cell damage through increased oxidative stress. This suggests TNF plays both an immunologic role in keratinocyte damage and also interferes with direct cellular injury. TNF also stimulates antiapoptotic pathways via nuclear factor- κ -B, and previous studies of patients treated with anti-TNF agent thalidomide showed increased mortality.⁹²

The first case of TEN treated satisfactorily with a single dose of infliximab (5 mg/kg) was published in 2002.⁹⁶ Since then, 12 more cases have been reported including a small case series of four patients in which two received only infliximab as treatment. Dose regimens used are either 5 mg/kg or a single 300 mg dose. The results are encouraging because most of the patients were reported to have favorable outcomes. Most of them received more than one treatment besides infliximab including IVIG.⁹⁷

Two single case reports of TEN treated with etanercept have been published in 2007 and 2009.^{98,99} More recently a series of 10 patients were treated with 50 mg of etanercept within the first 72 hours of the first manifestation of the disease (during the first 6 hours of hospitalization). None of the patients received any other treatment. All patients had a favorable outcome (improving the calculated SCORTEN for each case), there were no deaths, and reepithelization was completed in a median of 8.5 days.¹⁰⁰

INTRAVENOUS IMMUNOGLOBULIN

IV immunoglobulin (IVIG) comes in several formulations, including Carimune (ZLB Behring LLC, King of Prussia, Pennsylvania), Flebogamma (Instituto Grifols, SA, Barcelona, Spain), Gammagard (Baxter, Deerfield, Illinois), Gammar (Aventis Behring, King of Prussia, Pennsylvania), Gamunex (Talecris Biotherapeutics, Research Triangle Park, North Carolina), Octagam (Octapharma, Lachen, Switzerland), Panglobulin (ZLB Behring LLC), Polygam (Baxter), Gamimune (Talecris Biotherapeutics), Iivegam (Oesterreichisches Institut fuer Hemoderivate GmbH, OIH), Sandoglobulin (Novartis, Basel, Switzerland), and Venoglobulin (Alpha Therapeutic Corporation, Grifols USA, Los Angeles, California).

The mechanism of action of IVIG is not fully understood and may differ depending on the disease. The following mechanisms have been proposed: lowering the levels of deleterious autoantibodies through idiotypic antibodies contained in IVIG; accelerating the catabolism of pathogenic IgG by saturating neonatal Fc receptors (FcRns) with exogenous IgG; inhibiting the pathogenic activation of T lymphocytes by antibodies to CD4 and other T-cell receptors; inhibiting complement-mediated damage; interfering with the production, release, and function

of inflammatory cytokines including interleukins-2, -3, -4, -5, -6, and -10, TNF- α , and granulocyte-macrophage colony-stimulating factor; inhibiting the differentiation and maturation of dendritic cells, thereby reducing the activation of harmful T cells; increasing sensitivity to corticosteroids; and inhibiting thromboxane A₂ and endothelin, and increasing prostacyclin secretion.^{101,102}

Indications are primary and secondary immunodeficiencies (i.e., common variable immunodeficiency), X-linked agammaglobulinemia, severe combined immunodeficiency, Wiskott-Aldrich syndrome, acute and chronic immune thrombocytopenic purpura, human immunodeficiency virus (HIV) in children, chronic lymphocytic leukemia, Kawasaki disease, Guillain-Barré syndrome, and GVHD prophylaxis in patients receiving allogeneic bone-marrow transplantation.¹⁰³

Dosage

IVIG is composed of human plasma derived from pools of 1000–15,000 donors per batch. The purified immunoglobulin is stabilized with glucose, maltose, sucrose, mannitol, sorbitol, glycine, or albumin. IVIG is made up of more than 90% IgG and small amounts of IgM and IgA. Formulations may differ in IgA content, need for reconstitution, method of viral inactivation, osmolality, and sugar content. Generally, IVIG is given at a dose of 2 g/kg over 3–5 days, but it can be given over 2 days in younger patients with normal renal and cardiovascular function. The total amount of immunoglobulins that are infused with a 2 g/kg dose is enormous; serum IgG will increase approximately fivefold.^{101,102}

Mechanism of Action

The diseases covered in this chapter are inflammatory and immune mediated. Most of them require first-line treatments with immune-suppressive agents, such as corticosteroids or conventional agents. Biologic agents may exert, through specific targets, immunosuppressive actions. IVIG is not an immunosuppressive agent. Its mechanism of action depends on the disease that is being treated, but as a general rule, IVIG interferes with the action of pathogenic antibodies or cytokines by depleting its serologic concentrations or competing for its binding sites avoiding further proinflammatory actions.¹⁰²

Infusion-related side effects occur in less than 10% of patients and are generally mild and self-limiting. These side effects include headache, myalgias, flushing, fever, chills, fatigue, nausea or vomiting, low backache, chest discomfort, hypotension and hypertension, tachycardia, and such skin eruptions as dermatitis, urticaria, lichenoid reactions, palmar pruritus, and petechiae. Premedication with acetaminophen, nonsteroidal antiinflammatory agents, antihistamines, or low-dose IV corticosteroids may help avoid other infusion-related adverse events. Myalgias, chills, and chest discomfort may occur during the first hour and respond to halting the infusion for 30 minutes and then resuming it at a slower rate. Postinfusion fatigue, fever, or nausea may occur and last for 24 hours. More serious, but rare, adverse events include thromboembolic events; therefore, caution should be used in patients with risk factors for thromboembolism, immobilized patients, and patients with hyperviscosity syndromes. The U.S. Food and Drug Administration has identified high infusion rates and high doses as potential risk factors for thromboembolism in patients at risk. Hemolytic anemia may result from

blood group antibodies. Neutropenia is common, transient (lasting 2–14 days), and usually benign.¹⁰²

Transfusion-related acute lung injury is characterized by severe respiratory distress occurring 1–6 hours after the infusion. Aseptic meningitis occurs in 11% of patients receiving IVIG, particularly patients with a history of migraines. It usually presents with headache, meningismus, and photophobia. Severe anaphylactic reactions may occur in patients with IgA deficiency, because anti-IgA is produced in these patients and will react with the infused product. Acute tubular necrosis, which is usually reversible, may occur in individuals with preexisting renal disease and/or diabetes mellitus and in the elderly population. Acute tubular necrosis has been associated with IVIG products containing high concentrations of sucrose.¹⁰²

As with all blood products, there is a risk of transmission of viruses and prions. IVIG is screened for hepatitis B and C, HIV, and syphilis, and donors are carefully selected. Additional methods to remove viruses include physical inactivation with heat and chemical inactivation with solvents, low pH detergents, and caprylate. Caprylate and nanofiltration may also remove prions. Transmission of hepatitis B virus and HIV has not been reported. Transmission of hepatitis C virus has been reported and was likely a result of inadequate viral inactivation steps. The introduction of improved viral inactivation techniques, such as incubation at pH 4 and solvent-detergent treatment, should minimize this risk. In addition, there remains the risk of transmission of currently unidentified infectious agents.¹⁰²

Blistering Diseases

IVIG rapidly contributes to the decline of pathogenic autoantibody levels and disease activity. It is believed to act by several mechanisms:

- *Antiidiotypic antibodies:* These are antibodies directed against the variable regions of other antibodies. They are postulated to produce the rapid decline of pathogenic antibodies in autoimmune blistering diseases. The presence of these antibodies in IVIG was confirmed by studies in mice in which they inhibited acantholysis and deposition of IgG in intercellular spaces.
- *Neonatal Fc receptor:* This receptor is present in almost every cell and regulates the total serum IgG levels by protecting it from degradation. When saturated, IgG degradation increases. After IVIG both normal and pathogenic IgG rapidly decrease, but the latter is not replenished by IVIG therapy.
- *Inhibition of apoptosis:* The structural damage (acantholysis) and cell death (apoptosis) of keratinocytes are mediated by the same enzymes. IVIG inhibits this process by preventing suprabasal acantholysis and serving a protective role in TNF and FAS-mediated apoptosis.³⁸

There is general consensus that IVIG treatment is reserved for patients who fail conventional therapy, have contraindications to receiving it, or have rapidly progressive disease. It is also true that when it is used as adjuvant therapy with an immunosuppressive agent, response rates increase as compared to its use as a single agent. It has corticoid sparing effect and immunomodulatory effects.³⁸ A colleague in his study proposed the dose of 2 mg/kg divided in 3–5 days every 4 weeks

until disease control is obtained and then maintenance infusions are tapered every 6, 8, 10, 12, 14, and 16 weeks.¹⁰⁴

A synergistic combination is represented by IVIG and rituximab, since the former reduces pathogenic antibodies and the latter eliminates the pool of B cells destined to produce them.

Pemphigus Vulgaris

IVIG has been shown to be effective in the treatment of PV in numerous studies. IVIG lowers antibody titers to DSG 1 and DSG 3, often making them undetectable. In the two largest studies, which are from one institution, 42 patients were treated with IVIG (2 g/kg every 4 weeks) until control was achieved, as defined by healing of old lesions and no new lesions. The interval between IVIG treatments was then gradually increased to every 16 weeks. Prednisone and immunosuppressive agent (ISA) were tapered off during this time in all patients; IVIG was then used as monotherapy. Treatment with IVIG led to a clinical remission in all patients. In another study, control was achieved after a mean of 4.5 months, prednisone was tapered off after a mean of 4.8 months, and ISAs were tapered off after a mean of 2.9 months. Both studies were prospective but uncontrolled.^{105,106}

There have been an additional two case series and six case reports of the successful treatment of 23 patients with PV with IVIG. A juvenile case of PV had excellent response to IVIG.^{38,103}

In France, 12 patients with PV were treated with IVIG, and 8 were in complete remission at the end of treatment. In Mexico, a patient with refractory PV was treated with IVIG and healing of her mucosal and cutaneous lesions was seen in 3 weeks; however, IVIG was not always successful; nine case reports of treatment failures from other institutions have been reported. In one case, the patient received only one cycle of IVIG.^{38,103}

A study comparing the effect of a single cycle of IVIG in 61 patients with pemphigus receiving corticosteroids was made.¹⁰⁷ Forty-one patients were randomized to receive IVIG (200 and 400 mg/cycle) and 20 patients received placebo. The end point was the time the responding patients remained in the study. For the IVIG-treated patients, the time in the study was significantly longer, with improved clinical response and decrease in pathological antibodies.

Pemphigus Foliaceus

There is a prospective study of eight patients with severe (body surface area >30%) steroid-resistant PF. Patients were treated with IVIG (2 g/kg every 4 weeks) until they were completely healed. The interval between IVIG treatments was then gradually lengthened to every 16 weeks. All patients attained clinical control after a mean of 4 months. Prednisone was tapered off in a mean of 2.9 months; IVIG was used as monotherapy thereafter.¹⁰⁸

Eleven patients with PF were treated with IVIG (2 g/kg every 4 weeks) until they were completely healed. The interval between IVIG treatments was then gradually lengthened to every 16 weeks. All patients cleared after an average of 5.3 months of therapy. Prednisone was tapered off in a mean of 4.5 months and other ISAs after a mean of 2.6 months; IVIG was used as monotherapy thereafter. All 11 patients maintained remission after discontinuation of IVIG for a mean follow-up time of 18.6 months. A case of eyelid PF was also responsive to IVIG.¹⁰⁹

After that, additional case series also showed favorable outcome with more than 40 patients successfully treated.^{38,103}

Bullous Pemphigoid

There are more than 45 patients with BP treated with IVIG. Most cases are single reports or small retrospective series. In general clinical improvement is above 80% within 3 months. Most patients were unresponsive to conventional therapy.^{38,103}

In the only prospective study, 10 patients with BP were treated with IVIG (2 g/kg every 4 weeks).¹¹⁰ The interval between IVIG treatments was then gradually lengthened to every 16 weeks after patients cleared. All 10 patients cleared after a mean of 2.9 months and were able to discontinue prednisone after a mean of 3.3 months. IVIG was used as monotherapy thereafter. All patients achieved sustained remission with a mean duration of follow-up off IVIG of 22.9 months. Statistically significant decline in BP-180 and BP-230 autoantibodies was observed at 3 months. This decrease proved to be at a greater rate when IVIG was combined with another agent than when administered as monotherapy. The combination of IVIG and rituximab also appears to be beneficial as described in the study by Ahmed and colleagues.¹⁰⁹

Mucous Membrane Pemphigoid

MMP was treated with IVIG, leading to improvement in the disease in more than 78 patients. One patient had no response. IVIG has been shown to lower titers of β 4-integrin and α 6-integrin in patients with MMP.^{38,103}

IVIG was effective in the treatment of CP in several prospective studies from one institution. These patients were initially treated with corticosteroids and other ISAs, which were tapered off in all cases. Remission was generally attained in 4–5 months, and treatment with IVIG led to prolonged remissions that persisted after treatment with IVIG was discontinued. There have been two additional case reports of treatment successes and one treatment failure from other institutions.^{38,103}

The dose for MMP is higher than the one used in other blistering diseases (3 gr/kg/cycle every 2 weeks), especially for patients with ocular disease.³⁸

The combination of IVIG and rituximab could halt disease progression and prevent blindness as shown in a retrospective study.¹¹¹ Six patients were treated with this combination, and six patients received conventional immunosuppressive therapy. In the first group disease progression was arrested with visual sparing and all other six patients were blind by the end of the follow-up period.

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

The average reported mortality of patients with TEN in large series ranges between 25% and 35%. The mortality of patients with SJS is lower.⁹² Current treatment options are limited to supportive care in intensive care and burn units. Treatment with corticosteroids and other immunosuppressives is controversial and may result in higher incidences of complications secondary to sepsis, especially in TEN patients. The mechanism of action of IVIG in the treatment of TEN is not fully understood but may partially be explained by the observation that antibodies present in IVIG block Fas-mediated keratinocyte apoptosis in vitro. Because of the low prevalence of TEN, randomized controlled studies have not been performed.^{92,93,112}

The evidence for and against IVIG in the treatment of SJS and TEN consists of several prospective studies and multiple case records and series. The results are nonconclusive and contradictory. The majority of studies describe favorable outcomes,

but there is large variability between the study groups, which makes it harder to reach a conclusion. Overall, these studies found survival rates over 80%.⁹²

A large retrospective analysis of 281 SJS/TEN patients found 75 patients treated with IVIG with no improvement in mortality when compared to supportive therapy alone. They were treated with an average total dose of 1.5–1.9 gr/kg, which is lower than the one used in other series.¹¹³ Other studies reported poorer outcomes following IVIG treatment, though there are several limitations to these studies such as delayed treatment and low dosing.^{114,115}

In the first metaanalysis on the efficacy of IVIG in TEN, in the adult group, high doses correlated with low mortality; however, when multivariate analysis was applied, this was no longer valid. Pediatric TEN patients treated with IVIG had significantly lower mortality than adults.¹¹⁶

A subsequent metaanalysis included eight controlled and five smaller retrospective studies and found higher (>2 gr/kg) doses of IVIG inversely correlate with the standardized mortality rate calculated for these patients.¹¹⁷

Due to the lack of controlled, prospective, multicenter trials, strong conclusions regarding the effectiveness of IVIG in the treatment of TEN cannot be reached. Because IVIG is a biologic substance, there is variation in the final product between manufacturers and batch to batch that could affect results. For example, if interruption of Fas-mediated cell death by antibodies in IVIG is the mechanism of its action in TEN, then batches that are lacking these antibodies will not be successful; thus, the variability of different batches can account for the difference in results.

Although the results from the majority of case series support the use of IVIG in the treatment of TEN and TEN/SJS overlap, treatment with IVIG cannot be considered the standard of care in these cases.

OTHER DERMATOLOGIC EMERGENCIES TREATED WITH BIOLOGIC AGENTS

Erythrodermic Psoriasis

A retrospective multicenter study in France showed biologic therapy is effective in treating erythrodermic flares of moderate to severe plaque-type psoriasis or *de novo* erythrodermic psoriatic patients. The authors studied 28 patients, representing 42 acute erythrodermic episodes. The patients were treated with infliximab, etanercept, adalimumab, or efalizumab. Response rates of 75% improvement in PASI were observed in 40%–50% of the patients. Infliximab was the agent used as first-line therapy in most severe and urgent cases due to its rapid clearance of the lesions and high efficacy.¹¹⁸

Acute Generalized Pustulosis of Von Zumbusch

A 33-year-old man with a history of plaque-type psoriasis required amoxicillin for a tooth abscess. Three days later, he developed acute erythroderma with pustular lesions and was hospitalized in the intensive care unit. He was treated with 5 mg/kg infusion of infliximab with prompt resolution of the disease.¹¹⁹

Angioedema with Hypereosinophilia

A 54-year-old man with angioedema and hypereosinophilia was treated with prednisone (40 mg/d) and IVIG (400 mg/kg every 3 weeks). The patient had a marked decrease in symptoms

and eosinophil count after 6 weeks, after which prednisone was tapered off in 6 months. Interestingly, when the brand of IVIG was changed from Panglobulin to Gamimune N, the patient's illness recurred. Retreatment with Panglobulin led to remission again. This case report emphasizes the biologic variability that may exist between brands of IVIG.¹²⁰

CONCLUSIONS

Dermatologic emergencies are rare, life-threatening situations not often encountered by the physician. In this setting, conventional therapy remains more appropriate. Based on previous experience with biologic agents, these drugs are becoming an increasingly useful tool in refractory or relapsing cases. Rituximab and IVIG represent a very interesting option for blistering diseases, even as first-line therapy, and infliximab and etanercept show a promising future in SJS/TEN. New insights into disease pathogenesis open the repertoire to possible targets. The ability of these agents to target specific molecules is the key to improve the treatments offered to our patients without provoking sustained immunosuppression.

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Critical care: Stuff you really, really need to know

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All physicians should be experienced in the practices and procedures of basic life support (BLS) and advanced cardiopulmonary life support (ACLS). Outside the hallowed hospital walls, “Is there a doctor in the house?” means you! Within the hospital, the fundamental equipment and staff are on hand, but it is the responsibility of the nearest available physician to get it right and at maximum speed. The dermatology ward is no stranger to life-threatening events: This chapter is intended as a brief refresher course for the situations that cannot wait.

The ultimate goal of resuscitation is to maintain cerebral perfusion until and after cardiopulmonary functions are restored. Most adult cardiac arrests are due to ventricular arrhythmias for which early defibrillation is critical. The emphasis is on stabilizing the patient on site so that he or she can survive to get to an intensive care unit (ICU). The critically ill patients already on the ward are still not out of trouble, because they are usually being treated with many medications, leaving them vulnerable to adverse drug reactions, toxicity, and side effects, which themselves occur more frequently in these patients due to altered hemodynamics and metabolism. The high rate and rapid initiation of complications necessitate careful monitoring of vital signs and frequent physical examinations and laboratory tests. A high index of suspicion and close attention to changing symptoms and parameters are mandatory for preventing and/or treating any newly emerging medical problem. Routine care of a critically ill patient involves continuous assessment of symptoms, physical examination, hemodynamics, monitoring the need for changing the dose and/or route of administration of drugs, and constant vigilance in terms of the supportive care that is being administered.

Sedatives and analgesics are commonly administered to the critically ill patient. The clinician must recognize the diverse and often unpredictable effects of critical illness on the pharmacokinetics and pharmacodynamics of sedatives and analgesics. Failure to do so may lead to inadequate or excessive sedation. Bear in mind that sedatives and analgesics may cause prolonged alterations in mental status and may mask the development of coincident complications of critical illness.

The provision of resuscitation is based on medical guidelines, written by expert panels from many disciplines. They provide clear-cut instructions on the measures to be taken for treating life-threatening situations while allowing alterations in individual cases. Most importantly, the physician must rapidly and correctly recognize the nature of the emergent situation. To standardize treatment during resuscitation, a number of algorithms have been developed that were based on large studies and on laboratory and clinical evidence. These have been compiled into the American Heart Association (AHA) guidelines published and updated regularly.^{1,2} The most significant recent

changes were made to simplify cardiopulmonary resuscitation (CPR) instructions and increase the number of chest compressions delivered per minute while reducing the number of interruptions in chest compressions during CPR. After delivering two rescue breaths, the rescuer begins chest compressions immediately. A universal recommendation is to provide a single compression-to-ventilation ratio of 30:2. An important recommendation is that all rescue efforts—including insertion of an advanced airway, administration of medications, and reassessment of the patient—be performed in a way that minimizes interruption of chest compressions. *The most important determinant of survival from sudden cardiac arrest (SCA) is the presence of a trained rescuer who is ready, willing, able, and equipped to act.*

Unlike other medical interventions, CPR can be initiated without a physician's order, based on implied consent for emergency treatment. A physician's order, however, is necessary to withhold CPR. The decision to terminate resuscitative efforts rests with the treating physician in the hospital and is based on consideration of many factors, including time to CPR, time to defibrillation, comorbid disease, prearrest state, and initial arrest rhythm. Witnessed collapse, bystander CPR, and a short interval from collapse to the arrival of professionals improve the chances of a successful resuscitation. Local ethical and cultural norms must be considered when beginning and ending a resuscitation attempt: It behooves the physician to know what they are. Patients or families may ask physicians to provide care that is inappropriate. Physicians are not obliged to provide such care when there is scientific and social consensus against such treatment. One example is the administration of CPR for patients with the clear-cut signs of irreversible death. Whereas health-care providers are not obliged to provide CPR if no benefit from CPR and ACLS can be expected, few criteria can accurately predict the futility of CPR. In light of this uncertainty, all patients in cardiac arrest should receive resuscitation, unless the patient has a valid Do Not Attempt Resuscitation (DNR) order, if the patient has the standard signs of irreversible death, or if no physiological benefit can be expected, because vital functions have deteriorated despite maximal therapy.

BASIC LIFE SUPPORT

BLS includes recognition of life-threatening situations (such as SCA, heart attack, pulmonary embolism [PE], stroke, anaphylaxis, and foreign body airway obstruction [FBAO]) and the provision of rapid and effective CPR and defibrillation. SCA is a leading cause of death. Four critical points are important for the purpose of resuscitation: early recognition of the emergency situation, early CPR, early delivery of a shock, and early ACLS followed by postresuscitation care. The algorithm of BLS consists

* Deceased.

of the mnemonic *ABC*: *A* for airway, *B* for breathing, and *C* for circulation/compression. When a person lies unresponsive and without movement, check the airway and open it by the head tilt–chin lift maneuver. If the patient is not breathing, give two breaths. If there is a pulse, give breaths at a rate of 10–12 per minute and recheck the pulse every 2 minutes. If there is no central pulse, give a ratio of chest compressions to breaths of 30:2. The chest compressions should be on the lower half of the sternum at a rate of 100 per minute. It is important not to interrupt the chest compressions until the return of spontaneous rhythm/circulation (ROSC) or the arrival of a defibrillator: Chest compressions are preferable to ventilation when there is a single rescuer.

Supplementary oxygen should be used when available. When the victim has an advanced airway in place during CPR, two rescuers should no longer deliver cycles of CPR (compressions interrupted by pauses for ventilation). Instead, the compressing rescuer should administer continuous chest compressions at a rate of 100 per minute without pausing for ventilation. The rescuer delivering ventilation should provide 8 breaths per minute. If the rhythm can be altered by shock (e.g., a rapid heart rhythm), administer one shock with the highest energy and continue CPR immediately for five more cycles of 30:2. Recheck pulse and continue with shocks and CPR. If there is no pulse or the rhythm had not been suitable for applying shock, continue CPR and begin ACLS consisting of definitive breathing with intubation and the use of medications.

All BLS providers should be trained to provide defibrillation, because ventricular fibrillation (VF) is the most common rhythm found in adults with witnessed, nontraumatic SCA. For these victims, survival rates are highest when immediate bystander CPR is provided and defibrillation occurs within 3–5 minutes. The rescuer should intervene if the choking victim has signs of severe FBAO. These include signs of poor air exchange and increased breathing difficulty, such as a silent cough, cyanosis, or inability to speak or breathe. Do not interfere with the patient's spontaneous coughing and breathing efforts. Chest thrusts, back slaps, and abdominal thrusts are permissible and effective for relieving severe FBAO in conscious adults. If the adult victim with FBAO becomes unresponsive, the rescuer should carefully support the patient to the ground, and then begin CPR.^{3,4}

Cardiac Arrest

Cardiac arrest, defined as the sudden complete loss of cardiac output and therefore blood pressure, is the leading cause of death in the developed world. The mechanism of cardiac arrest in victims of trauma, drug overdose, drowning, and in many children is asphyxia. CPR with both compressions and rescue breaths is critical for resuscitation of these victims. In the majority of cases, the underlying etiology of arrest is myocardial ischemia in the setting of coronary artery disease. Conversely, cardiac arrest is the initial presentation of myocardial ischemia in approximately 20% of patients. A wide variety of other processes can lead to cardiac arrest, including septic shock, electrolyte abnormalities, hypothermia, PE, and massive trauma.

Survival from cardiac arrest remains low, even after the introduction of electrical defibrillation and CPR more than 50 years ago. In the best cases (witnessed VF arrest with rapid defibrillation), survival to hospital discharge is about 35%, although overall out-of-hospital arrest survival is usually much lower, about 15%. Several studies have documented the effects of time to defibrillation and the effects of bystander CPR on

survival from SCA. For every minute that passes between collapse and defibrillation, survival rates from witnessed VF-SCA decrease by 10% if no CPR is provided. If bystanders provide immediate CPR, many adults in VF can survive with intact neurological function, especially if defibrillation is performed within about 5 minutes after SCA. CPR prolongs VF (the window of time during which defibrillation can occur) and provides a small amount of blood flow that may maintain some oxygen to the heart and brain. Basic CPR alone, however, is unlikely to eliminate VF and restore a perfusing rhythm. Even after successful resuscitation from cardiac arrest, most patients die within 48 hours despite aggressive intensive care treatment.

CPR is important both before and after shock delivery. When performed immediately after collapse from VF-SCA, CPR can double or triple the victim's chance of survival. CPR should be provided uninterrupted until a defibrillator is available. After about 5 minutes of VF with no treatment, outcome may be better if defibrillation is preceded by a period of CPR with effective chest compressions that deliver some blood to the coronary arteries and brain. CPR is also important immediately after shock delivery: Most victims demonstrate asystole or pulseless electrical activity (PEA) for several minutes after defibrillation, and CPR can convert these rhythms to a perfusing rhythm. Most victims of SCA demonstrate VF, which is characterized by chaotic rapid complexes that cause the heart to tremble so that it is unable to pump blood effectively. Bear in mind that many SCA victims can survive if bystanders act immediately while VF is still present, but successful resuscitation is unlikely when the rhythm deteriorates to asystole. During cardiac arrest, basic CPR and early defibrillation are of primary importance, and drug administration is of secondary importance. After beginning CPR and defibrillation, rescuers can insert an advanced airway, establish intravenous (IV) access, and consider drug therapy. If spontaneous circulation does not return after defibrillation and peripheral venous drug administration, the provider may consider placement of a central line through the subclavian vein. When dealing with a pulseless arrest rhythm, begin BLS and CPR and call for help immediately. Attach defibrillator leads. VF or ventricular tachycardia (VT) are shockable rhythms. Give one shock (maximum energy) and continue five cycles of CPR with ACLS. Check again for rhythm and, if appropriate, give shock medications until return of a pulse. These medications are epinephrine (adrenaline) 1 mg IV every 3–5 minutes for three doses, or a single dose of vasopressin 40 U IV. After a second cycle of shocks and medications without response, consider the administration of amiodarone 300 mg IV, lidocaine IV at 1–1.5 mg/kg, and/or magnesium 1–2 g IV. If asystole is diagnosed, continue CPR while giving epinephrine or vasopressin as already mentioned, and consider atropine 1 mg IV every 3–5 minutes up to three doses. Check routinely for pulse or shockable rhythms and proceed accordingly, all the while bearing in mind that chest compressions must not be interrupted until ROSC. In adults with a prolonged arrest, shock delivery may be more successful after a period of effective chest compressions. There is insufficient evidence to recommend routine administration of fluids to treat cardiac arrest, but fluids should be infused if hypovolemia is suspected.^{5–9}

Finally, it is important to search for and treat possible reversible etiologies that are summarized as “6h's and 5t's”: *hypovolemia*, *hypoxia*, *hydrogen ion* (acidosis), *hypo/hyperkalemia*, *hypoglycemia*, *hypothermia*, *toxins*, *tamponade*, *tension pneumothorax*, *thrombosis* (coronary or pulmonary), and *trauma*.

Asystole and Pulseless Electrical Activity

PEA encompasses a heterogeneous group of pulseless rhythms. Pulseless patients with electrical activity have associated mechanical contractions, but these contractions are too weak to produce a blood pressure detectable by palpation or noninvasive blood pressure monitoring. PEA is often caused by reversible conditions (the 6h's and 5t's) and can be treated if those conditions are identified and corrected. Patients who have either asystole or PEA will not benefit from defibrillation attempts. The focus of resuscitation is to perform high-quality CPR with minimal interruptions and to identify reversible causes or complicating factors. Providers should insert an advanced airway. Rescuers should minimize interruptions in chest compressions while inserting the airway and should not interrupt CPR while establishing IV access. If the rhythm check confirms asystole or PEA, resume CPR immediately. A vasopressor (epinephrine or vasopressin) may be administered at this time. Epinephrine can be administered approximately every 3–5 minutes during cardiac arrest; one dose of vasopressin may be substituted for either the first or second epinephrine dose. For a patient in asystole or slow PEA, consider atropine. Do not interrupt CPR to deliver any medication. Give the drug as soon as possible after the rhythm check. After drug delivery and approximately five cycles (or about 2 minutes) of CPR, recheck the rhythm. If a shockable rhythm is present, deliver a shock. If no rhythm is present or if there is no change in the appearance of the electrocardiogram (ECG), immediately resume CPR. If an organized rhythm is present, try to palpate a pulse. If no pulse is present, continue CPR. If a pulse is present, the provider should identify the rhythm and treat accordingly. If the patient appears to have an organized rhythm with a good pulse, begin postresuscitative care.

Symptomatic Bradyarrhythmia or Tachyarrhythmia

Cardiac arrhythmias are a common cause of sudden death. ECG monitoring should be established as soon as possible for all patients who collapse suddenly or have symptoms of coronary ischemia or infarction. In general, if bradycardia produces signs and symptoms (acute alteration of mental status, ongoing severe ischemic chest pain, congestive heart failure, and hypotension) that persist despite adequate airway and breathing, prepare to provide pacing. For symptomatic high-degree atrioventricular (AV) block (second-degree AV block Mobitz type II and third-degree AV block) provide transcutaneous pacing without delay. If the tachycardic patient is unstable with severe signs and symptoms related to tachycardia, prepare for immediate cardioversion. If the patient with tachycardia is stable, determine if he or she has a narrow-complex or wide-complex tachycardia and then tailor therapy accordingly. In a patient with a heart rate lower than 60 beats per minute, which is inadequate for the clinical situation, check for airway and breathing and provide supplementary oxygen. Check vital signs, establish an IV access, and try to diagnose the bradyarrhythmia. If there are signs of adequate perfusion, observe and monitor the patient for the possibility of reversible causes with either later improvement or continuing deterioration. If there are signs of poor perfusion, call a cardiologist and begin to prepare for transcutaneous pacing, while considering atropine 0.5 mg IV for a total dose of 3 mg, and if the atropine is ineffective, begin to pace. Also consider epinephrine or dopamine by continuous drip while waiting for pacing. Use a temporarily external pacemaker if one is available. In conjunction with all of the above, identify and treat contributing factors (the 6h's and 5t's).

Atropine remains the first-line drug for acute symptomatic bradycardia. An initial dose of 0.5 mg, repeated as needed to a total of 3 mg, is effective in the treatment of symptomatic bradycardia. Transcutaneous pacing is usually indicated if the patient fails to respond to atropine, although second-line drug therapy with medications such as dopamine or epinephrine may be successful. Atropine will not suffice for infranodal blocks; they require a pacemaker. Other medications to consider are epinephrine (adrenaline), dopamine, or glucagon in the case of beta blocker or calcium channel blocker toxicity. Transcutaneous pacing is a class I intervention for any symptomatic bradycardia. It should be started immediately for patients who are unstable, particularly those with high-degree AV block.

After defibrillation and stabilization of the patient, the next step is to treat the factors that may have precipitated the tachycardia, if possible, such as fever, pulmonary emboli, hyperthyroidism, or acute myocardial infarction (MI). Supraventricular tachycardias (SVTs) with the pathophysiology of reentry will respond to carotid massage and/or adenosine 6 mg IV administration with abrupt cessation of the tachycardia. Other SVTs will necessitate slowing of the ventricular response by slowing the AV node conduction with IV medications such as beta blockers and/or calcium channel blockers and by trying to convert the rhythm to sinus rhythm if the tachyarrhythmia is not of long duration and there is a minimal risk of thromboembolism. Wide-complex tachycardias are often hemodynamically unstable and necessitate defibrillation. If the patient is stable (systolic blood pressure greater than 90 mm Hg, no angina pectoris, no altered mentation or signs of hypoperfusion), one can try IV medications. If there is the possibility of VT (note: any regular wide-complex tachycardia in an elderly person with a history of prior MI has a more than 80% chance of being VT), a trial of amiodarone or lidocaine is recommended. Amiodarone is given as a loading dose of 150 mg over 15 minutes and then in a 1200 mg maintenance drip over 24 hours. Lidocaine is given as a loading dose of 1–1.5 mg/kg slow push and then a maintenance drip of 2 g/day. If the diagnosis of VT is not possible, a trial of procainamide 20 mg every 1 minute should be considered until the tachycardia responds.

Although synchronized cardioversion is preferred for treatment of an organized ventricular rhythm, it is not possible for some arrhythmias. The many QRS configurations and irregular rates that comprise polymorphic VT make it difficult or impossible to reliably synchronize to a QRS complex. In addition, the patient with persistent polymorphic VT will probably not maintain perfusion/pulses for very long, so any attempt to distinguish between polymorphic VT with or without pulses quickly becomes doubtful. A good rule of thumb is that if your eye cannot synchronize to each QRS complex, neither can the defibrillator. If there is any doubt whether monomorphic or polymorphic VT is present in the unstable patient, do not delay shock delivery to perform detailed rhythm analysis—provide high-energy unsynchronized shocks. After shock delivery, be prepared to provide immediate CPR and follow the ACLS Pulseless Arrest Algorithm if pulseless arrest develops.

MEDICATION IN ACLS AND OTHER CARDIAC EMERGENT CASES

Epinephrine

Epinephrine produces beneficial effects in patients during cardiac arrest, primarily due to its adrenergic receptor-stimulating (vasoconstrictor) properties, which increase coronary and

cerebral perfusion pressure during CPR. The value and safety of the β -adrenergic effects of epinephrine are controversial, because they may increase myocardial work and reduce sub-endocardial perfusion. It is appropriate to administer a 1 mg dose of epinephrine IV every 3–5 minutes during adult cardiac arrest. If IV access is delayed or cannot be established, epinephrine may be given by the endotracheal route at a dose of 2–2.5 mg.

Vasopressin

Vasopressin is a nonadrenergic peripheral vasoconstrictor that also causes coronary and renal vasoconstriction. There are no significant differences between vasopressin and epinephrine for ROSC, 24-hour survival, or survival to hospital discharge. Because vasopressin effects have not been shown to differ from those of epinephrine in cardiac arrest, one dose of vasopressin 40 U IV may replace either the first or second dose of epinephrine in the treatment of pulseless arrest.

Atropine

Atropine reverses cholinergic-mediated decreases in heart rate, systemic vascular resistance, and blood pressure. It can be considered for asystole or PEA. The recommended dose of atropine for cardiac arrest is 1 mg IV, which can be repeated every 3–5 minutes (maximum total of three doses or 3 mg) if asystole persists.

Amiodarone

IV amiodarone affects sodium, potassium, and calcium channels as well as α - and β -adrenergic blocking properties. It can be considered for the treatment of VF or pulseless VT unresponsive to shock delivery, CPR, and a vasopressor. It improves survival rates and defibrillation response when given for VF or hemodynamically unstable VT.

Lidocaine

Lidocaine is an alternative antiarrhythmic of long-standing familiarity with fewer immediate side effects than may be encountered with other antiarrhythmics. Lidocaine, however, has no proven short- or long-term efficacy in cardiac arrest. It should be considered an alternative treatment to amiodarone. The initial dose is 1–1.5 mg/kg IV. If VF/pulseless VT persists, additional doses of 0.5–0.75 mg/kg IV push may be administered at 5- to 10-minute intervals, to a maximum dose of 3 mg/kg.

Magnesium

Magnesium can effectively terminate torsades de pointes (irregular/polymorphic VT associated with prolonged QT interval). It is not likely to be effective in terminating irregular/polymorphic VT in patients with a normal QT interval. The acute treatment is 1 to 2 g IV loading dose and a maintenance dose of 3–5 g/day. Care must be taken in renal failure and congestive heart failure, where those dosages should be halved, and serum magnesium level should be monitored.

Adenosine

Adenosine is an endogenous purine nucleoside that briefly depresses AV node and sinus node activity. It is recommended

for defined, stable, narrow-complex AV nodal or sinus nodal reentry tachycardias. Adenosine will not terminate arrhythmias, such as atrial fibrillation, atrial flutter, or atrial or ventricular tachycardias, because these arrhythmias are not caused by reentry involving the AV or sinus node. Adenosine has a short half-life. Its acute dose is 6 mg IV while monitoring the ECG. If there is no response within 3–5 minutes, a repeat dose of 12 mg IV should be tried, and then a third one by the same rules. Each dose of adenosine should be flushed with 20 cc of saline.

Calcium Channel Blockers: Verapamil and Diltiazem

Verapamil and diltiazem are nondihydropyridine calcium channel blocking agents that slow conduction and increase refractoriness in the AV node. These actions may terminate reentrant arrhythmias and control ventricular response rate in patients with a variety of atrial tachycardias. These medications are indicated for stable, narrow-complex, reentry mechanism tachycardias (reentry SVT) if rhythm remains uncontrolled or unconverted by adenosine or vagal maneuvers; for stable, narrow-complex, automaticity mechanism tachycardias if the rhythm is not controlled or converted by adenosine or vagal maneuvers; and for controlling the rate of ventricular response in patients with atrial fibrillation. Verapamil 2.5–5 mg is effective for terminating narrow-complex reentry SVT, and it may also be used for rate control in atrial fibrillation. Verapamil should be given only to patients with narrow-complex reentry SVT or arrhythmias known with certainty to be of supraventricular origin. It should not be given to patients with impaired ventricular function or heart failure.

Diltiazem seems to be equivalent in efficacy to verapamil. It is administered at a dose of 20 mg IV over 2 minutes, and repeated after 15 minutes at a dose of 25 mg. Verapamil and, to a lesser extent, diltiazem may decrease myocardial contractility and critically reduce cardiac output in patients with severe left ventricular dysfunction.

β -Adrenergic Blockers

Beta blocking agents (atenolol, metoprolol, labetalol, propranolol, esmolol) reduce the effects of circulating catecholamines and decrease heart rate and blood pressure. They also have various cardioprotective effects for patients with ACS. For acute tachyarrhythmias, these agents are indicated for rate control for narrow-complex tachycardias that originate from either a reentry mechanism (reentry SVT) or an automatic focus uncontrolled by vagal maneuvers and adenosine in the patient with preserved ventricular function, and to control the rate in atrial fibrillation and atrial flutter in the patient with preserved ventricular function. Commonly used drugs in the acute situation are propranolol 1 mg IV and metoprolol 5 mg IV. They can later be converted to oral propranolol 10 mg three times per day or oral metoprolol 25 mg twice a day, respectively. Side effects related to β -blockade include bradycardias, AV conduction delays, and hypotension. Cardiovascular decompensation and cardiogenic shock after β -adrenergic blocker therapy are infrequent complications. Contraindications to the use of β -adrenergic blocking agents include second- or third-degree heart block, hypotension, severe congestive heart failure, and lung disease associated with bronchospasm. These agents may be harmful for patients with atrial fibrillation or atrial flutter associated with known preexcitation (Wolff-Parkinson-White [WPW] syndrome).

Procainamide

Procainamide suppresses both atrial and ventricular arrhythmias by slowing conduction in myocardial tissue.

Procainamide is superior to lidocaine in terminating spontaneously occurring VT when given in doses of 100 mg IV every 5–10 minutes as tolerated, not to exceed 1000 mg. Procainamide may be considered in stable monomorphic VT in patients with preserved ventricular function, control of heart rate in atrial fibrillation or atrial flutter in patients with preserved ventricular function, acute control of heart rhythm in atrial fibrillation or atrial flutter in patients with known preexcitation (WPW) syndrome and preserved ventricular function, and for AV reentrant, narrow-complex tachycardias, such as reentry SVT if rhythm is uncontrolled by adenosine and vagal maneuvers in patients with preserved ventricular function.

OTHER EMERGENCIES

Foreign Body Airway Obstruction

Death from FBAO is uncommon but preventable. Most reported cases of FBAO in adults are caused by impacted food and occur while the victim is eating. Because recognition of airway obstruction is the key to successful outcome, it is important to distinguish this emergency from fainting, heart attack, seizure, or other conditions that may cause sudden respiratory distress, cyanosis, or loss of consciousness. When FBAO produces signs of severe airway obstruction, rescuers must act quickly to relieve the obstruction. If mild obstruction is present and the victim is coughing forcefully, do not interfere with his or her spontaneous coughing and breathing efforts. Attempt to relieve the obstruction only if signs of severe obstruction develop: The cough becomes silent, respiratory difficulty increases and is accompanied by stridor, or the victim becomes unresponsive. For responsive adults and children at least 1 year old with severe FBAO, case reports show the feasibility and effectiveness of back blows or “slaps,” abdominal thrusts, and chest thrusts. Although these maneuvers are feasible and effective for relieving severe FBAO in conscious adults and children at least 1 year of age, for simplicity in training, we recommend that the abdominal thrust be applied in rapid sequence until the obstruction is relieved. If abdominal thrusts are not effective, the rescuer may consider chest thrusts. It is important to note that abdominal thrusts are not recommended for infants younger than 1 year, because the thrusts themselves may cause injuries. Chest thrusts should be used for obese patients if the rescuer is unable to encircle the victim’s abdomen. If the choking victim is in the late stages of pregnancy, the rescuer should use chest thrusts instead of abdominal thrusts. If the adult victim with FBAO becomes unresponsive, the rescuer should carefully support the patient to the ground and then begin CPR. A health-care provider should use a finger sweep only when the provider can see solid material obstructing the airway of an unresponsive patient.

Pulmonary Embolism

PE is a life-threatening condition. The embolus usually derives from the deep veins of the leg or pelvis. Critically ill and bedridden patients are at high risk. Other common risk factors include thrombophilia and cancer. The main clues of an existing PE are dyspnea, tachypnea, tachycardia, low saturation, and sometimes pleuritic chest pain, in the above settings. The gold standard for diagnosis is computed tomographic (CT) angiography. The patient should be treated with oxygen and anticoagulation (e.g.,

subcutaneous [SC] enoxaparin 1 mg/kg twice a day, reduced to once daily if renal function is impaired). In severe life-threatening cases assessed clinically and/or echocardiographically, the treatment should be fibrinolysis (IV streptokinase 250,000 U bolus maintained at 100,000 U/h for up to 48–72 hours). To prevent PE, critically ill patients should be treated with anticoagulation prophylaxis while bedridden (SC enoxaparin 1 mg/kg once daily or SC heparin 5000–7500 U twice or thrice daily). Recurrent PE or contraindications to anticoagulation will necessitate the usage of an inferior vena caval filter.

Pulmonary Edema

Pulmonary edema is a life-threatening condition caused by both cardiogenic and noncardiogenic etiologies, such as acute MI, acute heart failure, hypertensive crisis, pulmonary emboli, or infections. The etiology must be sought and treated, in parallel with the administration of diuretics, vasodilators, and morphine, as needed. Recommended doses are IV furosemide 40 mg (or 60 mg in renal failure), IV nitroglycerin 1 mg/h and uptitrated as blood pressure permits (contraindicated if systolic blood pressure is <90 mm Hg), and IV morphine 3 mg, repeated as needed. A continuous positive airway pressure (CPAP) device and sometimes intubation will be needed until the patient is stabilized.

Myocardial Infarction

MI is primarily the consequence of atherothrombotic disease of the coronary arteries. Atherosclerosis of the coronary arteries is a common phenomenon in the vast majority of the population, and its occurrence coincides with “atherosclerotic risk factors,” for example, smoking, diabetes mellitus, hypertension, hyperlipidemia, and family history of premature coronary disease. Atherosclerotic plaques can disrupt blood flow caused by mechanical or inflammatory factors, and they can erode and rupture so that a thrombus evolves rapidly on top of them, thus atherothrombosis. Other etiologies of MI include embolization or spasm of the coronary artery. Many patients suffering an acute MI die instantly due to acute complications, such as malignant ventricular arrhythmia or mechanical failure of the heart. Others who reach the hospital need to be treated immediately to open the occluded coronary artery, either medically with thrombolytics or mechanically with percutaneous coronary intervention (PCI). Afterward, the patient must take medications for secondary prevention (aspirin, beta blockers, angiotensin-converting enzyme [ACE] inhibitors) and aggressively treat any modifiable risk factor.

A patient with risk factors and/or a prior coronary event who presents with typical chest pain must immediately be given chewable aspirin 300 mg, IV heparin 80 U/kg, and sublingual nitrate if his or her blood pressure is normal. An ECG must be immediately performed and interpreted: If it shows classical signs of ST elevation MI, the patient has to be prepared for immediate PCI. If the ECG is normal, the patient needs to be monitored, undergo repeat ECG, and have blood drawn for measuring troponin levels at 4–6 hours from the beginning of pain: A high troponin level means a non-ST elevation MI, and a normal value means acute coronary syndrome (ACS) or unstable angina pectoris (UAP). Either way, based on clinical and hemodynamic parameters and on noninvasive tests, a diagnostic coronary angiography will need to be performed to evaluate the need for revascularization.

Stroke

Stroke is the number three killer and a leading cause of severe, long-term disability. Fibrinolytic therapy administered within the first hours of the onset of symptoms contains neurological injury and improves outcome in selected patients with acute ischemic stroke. The window of opportunity is, however, extremely limited. Effective therapy requires early detection of the signs of stroke, appropriate evaluation and testing, and rapid delivery of fibrinolytic agents to eligible patients. The goal of stroke care is to minimize brain injury and maximize patient recovery. When there is suspicion of stroke, the goal of care is to perform the initial assessment within 10 minutes, performing and interpreting a CT scan within 25 minutes, and administering fibrinolytics to selected patients within 3 hours of the onset of symptoms. If the stroke patient is not eligible for fibrinolytic therapy and there is no suspicion of a hemorrhagic stroke (either by CT or clinically/anamnestically, such as no head trauma, no anticoagulation therapy, no uncontrolled hypertension or arteriovenous malformations), then the immediate treatment is high-dose aspirin. A rapid assessment of consciousness and neurological status is performed using the Glasgow Coma Scale, which is based on three parameters: eye movement, motor assessment, and verbal assessment. The scores range from 3 (poorest) to 15 (best). Any stroke victim with a score less than 8 needs airway protection with endotracheal intubation.

Patients with acute stroke are at risk for respiratory compromise from aspiration, upper airway obstruction, hypoventilation, and neurogenic pulmonary edema. The combination of poor perfusion and hypoxemia will exacerbate and extend ischemic brain injury, and has been associated with worse outcome from stroke. The administration of supplementary oxygen is mandatory.

A 12-lead ECG does not take priority over the CT scan, but it may identify a recent acute MI or arrhythmias (atrial fibrillation) as the cause of an embolic stroke. There is general agreement to recommend cardiac monitoring during the initial evaluation of patients with acute ischemic stroke to detect atrial fibrillation and potentially life-threatening arrhythmias. Management of hypertension in the stroke patient is controversial. For patients eligible for fibrinolytic therapy, however, control of blood pressure is required to reduce the potential risk of bleeding. If a patient who is otherwise eligible for treatment with tissue plasminogen activator (tPA) has elevated blood pressure, try to lower it to $<185/ <110$ mm Hg. Because the maximum interval from onset of stroke until effective treatment of stroke with tPA is limited, most patients with sustained hypertension above these levels cannot be treated with IV tPA. Fibrinolytic administration is not recommended if the patient's neurological signs appear to be clearing spontaneously and approaching baseline.

As with all medications, fibrinolytics have potential adverse effects. The physician must verify that there are no exclusion criteria, consider the risks and benefits to the patient, and be prepared to monitor and treat any potential complications. The major complication of IV tPA for stroke is symptomatic intracranial hemorrhage.

Hypertensive Crisis

Marked elevation of blood pressure to levels greater than 200/120 mm Hg requires immediate attention. The urgency and the method of treatment are not dictated solely by the

absolute level of blood pressure but also according to the patient's clinical status. The treatment is urgent if the patient is encephalopathic, pregnant with toxemia, or suffering from acute myocardial ischemia, aortic dissection, or acute stroke. Malignant hypertension is a clinical diagnosis manifested by systolic blood pressure greater than 220 mm Hg and/or diastolic blood pressure greater than 130 mm Hg with hemorrhagic retinopathy, papilledema, and other end-organ involvement, such as renal failure and encephalopathy. Clinically, the patient is likely to have pulmonary edema, in which case the treatment of choice will combine a diuretic (IV furosemide 40 mg) with a vasodilator (e.g., as nitroglycerin 1 mg/h and uptitrated or nitroprusside 0.3–10 µg/kg/min). Other maintenance therapies constitute thiazides (oral chlorothiazide 12.5 mg once daily), ACE inhibitors (e.g., oral enalapril 10 mg twice daily), central-acting drugs (oral aldimine 250 mg twice daily), and alpha (oral doxazosin 1–8 mg once daily), beta (oral metoprolol 25 mg twice daily), and/or calcium blockers (oral amlodipine 5 mg once daily). The aim of urgent treatment is to lower the blood pressure by not more than 25% so as not to impair cerebral blood flow. Practically, the drug regimen should contain IV furosemide 40 mg push and IV nitroglycerin 20 mg/100 mg saline (beginning 2 cc/h rate, uptitrated as needed). Consider a beta blocker (also exerting alpha-blocking effects) such as labetalol at an initial IV dose of 20 mg injected over 2 minutes and additional injections of 40 or 80 mg every 10 minutes as needed up to a total dose of 300 mg. Another possibility is an agent with direct vasodilator properties, such as nitroprusside with a starting dosage of 0.1 g/kg/min and increased as necessary and as tolerated.

Shock

Shock is a syndrome of low blood pressure and inadequate end-organ perfusion. Its main etiologies are cardiogenic, septic, hemorrhagic, and anaphylactic. Cardiogenic shock must be considered in a patient with a history of heart disease who presents with chest pain and low blood pressure with peripheral hypoperfusion. In such a patient, the shock is most probably due to acute MI and/or acute heart failure. As such, treatment will constitute revascularization with either PCI or coronary artery bypass grafting and inotropic drugs (e.g., IV dopamine 400 mg/500 cc saline in an initial rate of 5 cc/h, or IV dobutamine 500 mg/500 cc saline, in an initial rate of 5 cc/h). Septic shock is probable in a patient with fever, chills, and infection; the patient must be treated with fluids, antibiotics, and glucocorticoids for adrenal insufficiency. Patients who have lost blood must be treated with a blood transfusion. Anaphylactic shock is due to drugs or toxins, and the immediate treatment is SC adrenaline 0.1 mg and the usual supportive treatment.

SPECIAL PROCEDURES

Endotracheal Intubation

The endotracheal tube confirms a patent airway, permits suctioning of airway secretions, enables delivery of a high concentration of oxygen, provides an alternative route for the administration of some drugs, facilitates delivery of a selected tidal volume, and, with the use of a cuff, may protect the airway from aspiration. Endotracheal intubation attempts by unskilled providers can produce complications such as trauma to the oropharynx, interruption of compressions and ventilations for unacceptably long periods, and hypoxemia from

prolonged intubation attempts or failure to recognize tube misplacement or displacement. Indications for emergency endotracheal intubation are the inability of the rescuer to adequately ventilate the unconscious patient with a bag and mask and the absence of airway protective reflexes (coma or cardiac arrest).

During CPR, the rescuers should minimize the number and duration of interruptions in chest compressions, with the goal of limiting interruptions to no more than 10 seconds except as needed for interventions, such as placement of an advanced airway. Interruptions needed for intubation can be minimized if the intubating rescuer is prepared to begin the intubation attempt as soon as the compressing rescuer pauses in administering compressions. The compressions should be interrupted for only as long as the intubating rescuer needs to visualize the vocal cords and insert the tube. The compressing rescuer should be prepared to resume chest compressions immediately after the tube is passed through the vocal cords. If more than one intubation attempt is required, the rescuers should provide a period of adequate ventilation and oxygenation and chest compressions between attempts. If endotracheal intubation is performed for the patient with a perfusing rhythm, use pulse oximetry and ECG monitoring continuously during intubation attempts and interrupt the attempt to provide oxygenation and ventilation if needed.

Even when the endotracheal tube is seen to pass through the vocal cords and tube position is verified by chest expansion and auscultation during positive-pressure ventilation, rescuers should obtain additional confirmation of placement by using an end-tidal CO₂ or esophageal detection device. The most important caveats for rescuers performing CPR after insertion of the advanced airway are to be sure the advanced airway is correctly placed and to not cease CPR efforts.

Complications of endotracheal intubation are associated with improper endotracheal tube positioning. Esophageal and right main stem bronchus intubation should be suspected if hypoxemia, hypoventilation, or cardiac decompensation occurs. Abdominal distension, lack of breath sounds over the thorax, and regurgitation of stomach contents indicate esophageal intubation. In emergency settings when standard endotracheal intubation cannot be performed, needle cannulation of the cricothyroid membrane can be performed as a stopgap before providing a more definitive airway.

Central Venous Catheterization

Central venous catheterization is the insertion of an indwelling catheter to a large central vein, mostly the subclavian or internal jugular veins. It is mainly indicated for better fluid therapy, drug administration, and parenteral nutrition, and for monitoring of the central venous pressure. The only contraindication against its use is an existing coagulopathy.

Postresuscitation Support

The management of successfully resuscitated patients should focus on the treatment of the underlying disease process and the maintenance of electrical, hemodynamic, and respiratory stability. All patients require careful repeated assessment and should be initially monitored in an ICU. Few randomized, controlled clinical trials have dealt specifically with supportive care following cardiopulmonary-cerebral resuscitation from cardiac arrest; nevertheless, postresuscitation care has significant potential to improve early mortality caused by hemodynamic

instability and multiorgan failure and later mortality/morbidity resulting from brain injury.

The initial objectives of postresuscitation care are to optimize cardiopulmonary function and systemic perfusion, especially perfusion to the brain, and to continue care in an appropriately equipped critical care unit. Attempts are made to identify the precipitating causes of the arrest, and measures are instituted to prevent recurrence and improve long-term, neurologically intact survival.

Induced Hypothermia

Both permissive hypothermia (allowing a mild degree of hypothermia >33°C that often develops spontaneously after arrest) and active induction of hypothermia may play a valuable role in postresuscitation care. Hypothermia resulted in improved outcome in adults who remained comatose after initial resuscitation from cardiac arrest.^{10,11} Complications associated with cooling may include coagulopathy and arrhythmias, particularly with an unintentional drop below target temperature. There was some increase in the number of cases of pneumonia and sepsis in the hypothermia-induction group. Cooling may also increase hyperglycemia. Mild hypothermia may be beneficial to neurologic outcome and is likely to be well tolerated without significant risk of complications.

Glucose Control

The postresuscitation patient is likely to develop electrolyte abnormalities that may be detrimental to recovery. Many studies have documented a strong association between high blood glucose after resuscitation from cardiac arrest and poor neurologic outcomes. Tight control of blood glucose using insulin reduced hospital mortality rates in critically ill patients who required mechanical ventilation. Signs of hypoglycemia are less apparent in comatose patients, so clinicians must monitor serum glucose closely to avoid hypoglycemia when treating hyperglycemia. On the basis of findings of improved outcomes in critically ill patients, when glucose levels are maintained in the normal range, it makes sense to maintain strict glucose control during the postresuscitation period.

Organ-Specific Evaluation and Support

After ROSC, patients may remain comatose or have decreased responsiveness for a variable period of time. If spontaneous breathing is absent or inadequate, mechanical ventilation via an endotracheal tube or other advanced airway device may be required. Hemodynamic status may be unstable when there are abnormalities of cardiac rate, rhythm, systemic blood pressure, and organ perfusion. Clinicians must prevent, detect, and treat hypoxemia and hypotension, because these conditions can exacerbate brain injury. It is essential to determine the baseline postarrest status of each organ system and support impaired organ function as needed.

Respiratory System

Respiratory dysfunction is not uncommon after ROSC. Some patients will remain dependent on mechanical ventilation and will need an increased inspired concentration of oxygen. They should undergo a full physical examination as well as a chest x-ray to verify appropriate endotracheal tube depth of insertion and to identify any cardiopulmonary complications

of resuscitation. Mechanical ventilatory support should be adjusted based on the patient's blood gas values, respiratory rate, and work of breathing. As the patient's spontaneous ventilation becomes more efficient, the level of respiratory support may be decreased until spontaneous respiration returns. If the patient continues to require high inspired oxygen concentrations, providers should determine if the cause is pulmonary or cardiac and take measures accordingly. There is some debate as to the length of time that patients who require ventilatory support should remain sedated. To date, there is little evidence to guide therapeutic scheduling and inadequate data to recommend for or against the use of a defined period of sedation or neuromuscular blockade after cardiac arrest. Use of neuromuscular blocking agents should be kept to a minimum, because they preclude thorough neurologic assessments during the first 12–72 hours after ROSC.

Sustained hypocapnia may reduce cerebral blood flow. After cardiac arrest, restoration of blood flow results in an initial hyperemic blood flow response, followed by a more prolonged period of low blood flow. During this latter period of late hypoperfusion, there may be a mismatch between blood flow and oxygen requirement. If the patient is hyperventilated at this stage, cerebral vasoconstriction may further decrease cerebral blood flow and increase cerebral ischemia and ischemic injury. There is no evidence that hyperventilation protects the brain or other vital organs from further ischemic damage after cardiac arrest.

In summary, although there are no data to support targeting a specific arterial PaCO₂ level after resuscitation from cardiac arrest, data extrapolated from patients with brain injury support ventilation to reach normocarbic levels. Routine hyperventilation is detrimental.

Cardiovascular System

Both the ischemia/reperfusion of cardiac arrest and electrical defibrillation can cause transient myocardial stunning and dysfunction that can last many hours but may improve with vasopressors. Cardiac biomarker levels may be increased in association with global ischemia caused by absent or decreased coronary blood flow during cardiac arrest and CPR. Increased cardiac biomarkers may also indicate acute MI as the cause of cardiac arrest.

Hemodynamic instability is common after cardiac arrest, and early death caused by multiorgan failure is associated with a persistently low cardiac index during the first 24 hours after resuscitation. Thus, after successful resuscitation, clinicians should evaluate the patient's ECG, radiographs, and laboratory analyses of serum electrolytes and cardiac biomarkers. Performing an ECG within the first 24 hours after arrest is useful to guide ongoing management. Patients who are resuscitated following out-of-hospital cardiac arrest may have significant early but reversible myocardial dysfunction and low cardiac output, followed by later vasodilation. Hemodynamic instability usually responds to fluid administration and vasoactive support. Invasive monitoring may be necessary to measure blood pressure accurately and to determine the most appropriate combination of medications to optimize blood flow and distribution. The provider should titrate volume administration and vasoactive (e.g., norepinephrine), inotropic (e.g., dobutamine), and vasodilator (e.g., milrinone) drugs that are given to support blood pressure, cardiac index, and systemic perfusion. Both cardiac arrest and sepsis are thought to involve

multiorgan ischemic injury and microcirculatory dysfunction. Goal-directed therapy with volume and vasoactive drug administration has been effective in improving survival from sepsis. The greatest survival benefit is due to a decreased incidence of acute hemodynamic collapse, a challenge also seen in the postresuscitation setting. Relative adrenal insufficiency may develop following the stress of cardiac arrest, but the use of early corticosteroid supplementation in such patients to improve either hemodynamics or outcome is unproven and requires further evaluation. Although SCA may be precipitated by cardiac arrhythmia, it is unclear if antiarrhythmics are beneficial or detrimental in the postresuscitation period. Thus, there is insufficient evidence to recommend for or against prophylactic administration of antiarrhythmic drugs to patients who have survived cardiac arrest from any cause. It may be reasonable, however, to continue an infusion of an antiarrhythmic drug that was associated with ROSC. Also, given the cardioprotective effects of beta blockers in the context of ischemic heart disease, the use of beta blockers in the postresuscitation setting seems prudent if there are no contraindications.

Central Nervous System

A healthy brain and a functional patient are the primary goals of cardiopulmonary-cerebral resuscitation. Following ROSC, cerebral blood flow is reduced after a brief initial period of hyperemia (the "no-reflow phenomenon") as a result of microvascular dysfunction. This reduction occurs even when cerebral perfusion pressure is normal. Neurological support for the unresponsive patient should include measures to optimize cerebral perfusion pressure by maintaining a normal or slightly elevated mean arterial pressure and reducing intracranial pressure if it is elevated. Because hyperthermia and seizures increase the oxygen requirements of the brain, hyperthermia must be controlled, and therapeutic hypothermia should be considered.¹⁰

PROGNOSTIC FACTORS

The period after resuscitation is often stressful to medical staff and family members as questions arise about the patient's ultimate prognosis. Ideally, a clinical assessment, laboratory test, or biochemical marker would reliably predict the outcome during or immediately after cardiac arrest. Unfortunately, no such predictors are available. Determination of prognosis based on initial physical examination can be difficult, and coma scores may be less predictive than individual motor and brainstem reflexes found in the first 12–72 hours after arrest.

Five clinical signs that were found to strongly predict death or poor neurological outcome, with four of the five predictors detectable at 24 hours after resuscitation, are absent corneal reflex at 24 hours, absent pupillary response at 24 hours, absent withdrawal response to pain at 24 hours, no motor response at 24 hours, and no motor response at 72 hours. An electroencephalogram performed more than 24–48 hours after resuscitation also has been shown to provide useful predictive information and can help define prognosis.¹¹

Other Complications

Sepsis is a potentially fatal postresuscitation complication. Patients with sepsis will benefit from goal-directed therapy. Renal failure and pancreatitis, although often transient, should be ruled out.

MONITORING

Blood Pressure

Blood pressure can be monitored either noninvasively or invasively, and it is fundamental for hemodynamic assessment. When intraarterial monitoring is in place during the resuscitative effort (in an intensive care setting), the clinician should try to maximize arterial diastolic pressures to achieve an optimal coronary perfusion pressure.

Pulses

Arterial pulses should be palpated during chest compressions to assess the effectiveness of compressions. No studies have shown the validity or clinical utility of checking pulses during ongoing CPR. Carotid pulsations during CPR do not indicate the efficacy of coronary blood flow or myocardial or cerebral perfusion during CPR.

Arterial Blood Gases

Arterial blood gas monitoring during cardiac arrest is not a reliable indicator of the severity of tissue hypoxemia, hypercarbia (and therefore the adequacy of ventilation during CPR), or tissue acidosis. It provides the foundation for the assessment of respiratory function.

Oximetry

During cardiac arrest, pulse oximetry will not function, because pulsatile blood flow is inadequate in peripheral tissue beds, which are also constricted. It is, however, commonly used in emergency departments and critical care units for monitoring patients who are not in arrest, because it provides a simple, continuous method of tracking oxyhemoglobin saturation. Normal pulse oximetry saturation, however, does not ensure adequate systemic oxygen delivery.

End-Tidal CO₂ Monitoring

End-tidal CO₂ monitoring is a safe and effective noninvasive indicator of cardiac output during CPR and may be an early indicator of ROSC in intubated patients. CO₂ continues to be generated throughout the body during cardiac arrest. In the patient with ROSC, continuous or intermittent monitoring of end-tidal CO₂ provides assurance that the endotracheal tube is maintained in the trachea. End-tidal CO₂ can guide ventilation, especially when correlated with the PaCO₂ from an arterial blood gas measurement.

Sedatives

Sedatives and analgesics used commonly in the care of critically ill patients often exhibit pharmacokinetics and pharmacodynamics that are significantly different than those that are exhibited in studies of their use in other settings. Knowledge of these differences is crucial to designing a sedation protocol for the critically ill patient. Intravascular catheters, endotracheal intubation, suctioning, immobility, and underlying illnesses all may cause pain in the critically ill patient. Most patients require

IV narcotics at least initially (IV morphine 3 mg or IV fentanyl 12.5 µg). Thus, adequate sedation begins with adequate analgesia. Regional pain control techniques, such as with epidural catheter-administered anesthetics or opiates, can be highly effective at achieving pain control in the postoperative patient. The evaluation of sedation adequacy can be performed only at the bedside and is facilitated by use of validated sedation scales, along with a protocol for the systematic assessment and administration of sedatives and analgesics. Most postarrest patients require larger doses of sedatives in the initial 48 hours. Thus, the level of sedation must be reassessed continuously and a protocol for downward titration of sedation applied. If continuous administration is used, daily sedative interruption is recommended to prevent drug accumulation, to allow the performance of a neurological examination, and to permit reassessment of the need for sedation. An example of a sedative is oxazepam 10 mg thrice daily.

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Acute skin failure

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INTRODUCTION

Acute skin failure (ASF) is an emergency state encountered by dermatologists, akin to other organ failures. ASF does not imply simple disruption of cutaneous integrity and functional loss, but it also is a multiorgan failure. Although many authors have attempted to define ASF in various ways, the definition given by Irvine in 1991 appears most comprehensive: "Loss of normal temperature control with inability to maintain the core body temperature, and failure to prevent percutaneous loss of fluid, electrolytes and protein, with resulting imbalance, and failure of the mechanical barrier to prevent penetration of foreign materials."¹

A similar but better-studied condition is "burn injury." In some patients with ASF (e.g., Stevens–Johnson syndrome/toxic epidermal necrosis [SJS–TEN]), the skin involvement is similar to superficial burn. Most of the understanding of ASF to date is from the evidence drawn from burn patients.

Some authors have considered "pressure ulcer" as a form of skin failure and has categorized it as "acute," "chronic," and "end stage" based on chronicity of patients' underlying illness, a state of hypoperfusion, and presence or absence of risk factors for developing pressure ulcers.^{2,3}

The discussion in this chapter will be restricted to ASF due to widespread cutaneous disorder and multiorgan involvement.

EVOLUTION OF THE CONCEPT

When Sam Shuster from Newcastle on Tyne, United Kingdom, delivered the "Parkes Weber Lecture" at the Royal College of Physicians of London, on "Systemic effects of skin disease" in 1967,⁴ he became the first dermatologist to relate disturbed thermoregulation, anemia, hypoalbuminemia, and hemodynamic disturbances to erythroderma.⁴ His pioneering work on systemic effects of skin disease is the basis for the concept of skin failure. Catriona Irvine in 1991 defined skin failure as a real entity comparable to any other major organ dysfunction.¹ In the same year, Terence J. Ryan of Oxford, United Kingdom, also described skin failure as one of the causes of disability in dermatology.⁵

Jean-Claude Roujeau of Paris mentioned the term "acute skin failure" in a paper to describe the systemic effects of TEN.⁶ He pleaded for the management of such cases to be in specialized "dermatology intensive care units (DICU)" rather than in burn units.

CAUSES

Morphologically, we propose to categorize underlying causes of ASF as "dry disorders," i.e., disorders giving rise to erythroderma and "wet disorders," i.e., vesiculobullous disorders.

Such categorization has practical implications, as hemodynamic alterations, extent of fluid, electrolyte, and nutrient-loss and management aspects may differ in these two broad types. Various underlying dermatologic disorders giving rise to ASF are presented in Table 6.1.⁷ The list is comprehensive but not exhaustive.

ALTERED PHYSIOLOGY IN PATIENTS WITH ASF Hemodynamic Changes

In patients with ASF, there are vasodilatation and enhanced blood flow to the chronically inflamed skin (normal 0.5–1 L/min versus 5 L/min).⁸ Clinically, it is evident as bright erythema and edema of the skin (Figure 6.1). This leads to increased cardiac output (normal 5 L/min versus >10 L/min) and venous return.⁸ There are tachycardia and decreased perfusion to the vital organs. In case of preexisting functional compromise, there is risk of sudden cardiac or renal failure.

High levels of vascular permeability factor (VPF) and vascular endothelial growth factor (VEGF) have been detected in patients with erythroderma of long duration. These make capillary leakage, causing expansion of extracellular space and resultant dependent edema.⁹ Various causes of peripheral edema are presented in Box 6.1.

Though patients with ASF are in a "high-cardiac-output" state, hypovolemic shock may occur due to dehydration and septicemia.

Altered Temperature Regulation

Temperature regulation of the body is an energy-consuming process partially achieved at the cost of calorie expenditure. Cutaneous blood circulation and evaporation of eccrine sweat are the two principal mechanisms for thermoregulation in the human body.⁸ About 200–300 mL of eccrine sweat is produced per day, and it evaporates from the skin surface.⁸ This, along with transepidermal water loss (TEWL), consumes 600 Kcal/L of fluid loss.⁸ Cutaneous vasculature is a complex network, specially designed in several layers to regulate body temperature. About 15%–20% of cardiac output flows through cutaneous vessels⁸ and maintains the surface temperature balanced between environmental and core body temperatures.

In the state of ASF, both the mechanisms are jeopardized. There is increased cutaneous blood flow, and sweat glands are either occluded or damaged in patients with long-standing erythroderma.¹⁰ Increased cutaneous blood flow leads to enhanced heat loss from the body surface leading to hypothermia. To maintain core body temperature, the patient starts shivering at the cost of a raised basal metabolic rate (BMR). When there is failure to compensate, core body temperature becomes equal to that of environment (poikilothermia).¹⁰

Table 6.1 Causes of Acute Skin Failure⁷

1. Erythroderma (dry disorders):
 - Congenital causes
 - Congenital ichthyosis (syndromic and nonsyndromic) (Figure 6.2)
 - Leiner disease
 - Acquired causes
 - Psoriatic erythroderma (Figure 6.3)
 - Acute generalized pustular psoriasis of Von Zumbush (Figure 6.4)
 - Pityriasis rubra pilaris
 - Atopic and other dermatitides
 - Crusted scabies
 - Drug-hypersensitivity syndrome (DHS) (Figure 6.5)
 - Pemphigus foliaceus (Figure 6.6)
 - Collagen vascular disorders (acute cutaneous lupus erythematosus, dermatomyositis)
 - Paraneoplastic (lymphoma, leukemia, solid organ tumors)
 - Langerhans cell histiocytosis
 - Erythrodermic sarcoidosis
 - Graft versus host disease
 - Idiopathic
2. Vesiculobullous disorders (wet disorders):
 - Genetic disorders
 - Epidermolysis bullosa
 - Bullous congenital ichthyosiform erythroderma
 - Acquired disorders
 - Immunobullous disorders
 - Hailey-Hailey disease (generalized form)
 - Drug-induced; SJS (Figure 6.7), TEN (Figure 6.8)
 - Staphylococcal scalded skin syndrome (SSSS)
 - Bullous mastocytosis

**Figure 6.1** Generalized erythema in a patient with acute skin failure. Also note mild ectropion.**Box 6.1 Various Causes of Peripheral Edema in Patients with ASF**

- Peripheral vasodilatation
- Capillary leakage
- Edema associated with the original inflammatory condition (e.g., SJS-TEN, psoriatic erythroderma)
- Hypoalbuminemia
- Associated cardiac failure
- Associated renal failure
- Fluid overload during resuscitation

**Figure 6.2** Congenital ichthyosiform erythroderma.**Figure 6.3** Psoriatic erythroderma in a child.

Rarely, extensive skin loss and release of interleukin-1 from necrotic keratinocytes may induce hyperthermia in these patients. Mechanical factors, such as occlusion of sweat ducts in patients with long-term erythroderma, may also give rise to hypohidrosis and hyperthermia.¹⁰



Figure 6.4 Acute generalized pustular psoriasis with lakes of pus.



Figure 6.5 Drug hypersensitivity syndrome.



Figure 6.6 (a–c) Erythroderma due to pemphigus foliaceus.

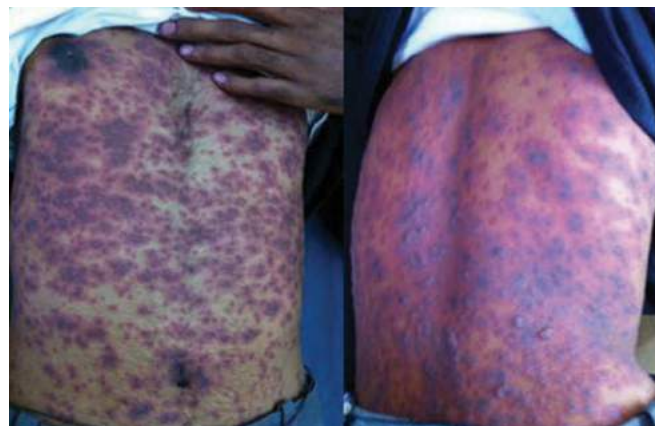


Figure 6.7 Stevens–Johnson syndrome.



Figure 6.8 Toxic epidermal necrolysis.

Altered Fluid and Electrolyte Balance

Composition and Distribution of Body Fluids in Health

Water is the major constituent of the human body comprising approximately 50% (women) to 60% (men) of body weight. Total body water is distributed into two major compartments, intracellular fluid (ICF) and extracellular fluid (ECF). The former constitutes 55%–75%, and the latter 25%–45% of the total body water.¹¹ The total volume of ECF in an adult is 270 mL/kg and is distributed in plasma and lymph (55 mL/kg), muscle and organs (85 mL/kg), and skin and connective tissue (130 mL/kg).¹² Skin constitutes a major reservoir of ECF in the form of interstitial fluid.

Osmotic equilibrium between ECF and ICF is important for normal functioning of cells. To maintain the equilibrium, osmolality of both ECF and ICF should be equal. It is achieved by movement of water across the cell membrane. The osmolality of the fluid is determined by the solute or particle concentration. The major ECF particles are Na^+ , Cl^- and HCO_3^- , whereas K^+ , adenosine triphosphate (ATP), creatinine phosphate, and phospholipids are major ICF particles. The number of intracellular particles remains constant as these are required for normal cell function. Therefore, the changes in ICF osmolality are due to changes in ICF water content.¹¹ To maintain homeostasis, the intake of water should be equal to its excretion. Normally, a measurable amount of water is lost through the kidneys and gastrointestinal tract; however, additional water is lost through evaporation from the skin and respiratory tract. Typically, the latter two are not measured and are termed as insensible water loss (IWL). TEWL contributes 70% of IWL.¹³ The normal composition and distribution of body fluids and TEWL vary depending on age groups and climatic conditions like humidity and temperature. These factors should also be considered along with underlying pathological changes during fluid resuscitation.

Fluid and Electrolyte Balance in Children

The percentage of total body water in fetal life gradually reduces with gestational age, from around 86% at 26 weeks to 80% at 32 weeks and to about 78% at full term.¹⁴ Neonates have high body surface area (BSA) to weight ratio and functionally immature kidneys. As compared to adults, infants and younger children have a larger daily turnover of water, relative to the total body water and large ECF space. All of these factors predispose children to a greater risk of fluid and electrolyte imbalance than adults.¹⁵

Fluid and Electrolyte Balance in Elderly

The percentage of water content of the body depends on lean body mass. With age, the lean body mass decreases resulting in decreased body water content; hence, fluid balance in the elderly requires special considerations. The fluid balance in the elderly is further compromised by decreased intake of food and water due to loss of appetite and thirst, physical dependence, and biochemical changes of aging. All of these factors result in increased susceptibility of the elderly to fluid deprivation. It has been reported that mortality associated with disturbances in water balance in the elderly may be as high as 40%–70%.¹⁶

Nature of Fluid and Electrolyte Imbalance in ASF

The composition and amount of fluid loss differ depending on type and severity of diseases causing acute skin failure. In diseases presenting as erythroderma (dry disorders), the

TEWL leads to hypernatremic dehydration, whereas in diseases presenting with extensive erosions (wet disorders) both water and electrolytes are lost. In addition, fever, sepsis, and comorbid conditions involving the central nervous system and kidneys put the patient at risk of fluid and electrolyte imbalance.

Fluid Loss in TEN

In adult patients with TEN involving >50% total body surface area (TBSA), the daily fluid loss exceeds 3–4 liters.¹⁷ The blister fluid of autoimmune bullous disorders and TEN contains approximately 120–150 mmol/L of Na^+ , 100 mmol/L of Cl^- , and 5–10 mmol/L of K^+ .¹⁸ The composition of blister fluid of pediatric patients with TEN was found to be similar to that of burns, except that the latter has a threefold higher albumin and protein. The lactate dehydrogenase, calcium, and magnesium were significantly high in both blister fluid specimens when compared to serum levels.¹⁹

Fluid Loss in Erythroderma

The TEWL in a child with ichthyosis ranges from 746 ± 468 mL/day (mean basal TEWL of 39.6 ± 20.6 mL/m²/hour compared to upper limit of normal 8.7 mL/m²/hour) to 209 mL/day seen in age-matched children with competent skin barrier.²⁰ An estimation of TEWL from normal and abnormal skin of a colloidion baby using evaporimeter at day 4 demonstrated a loss of 18 ± 2 g/m²/hour and 112 ± 2 g/m²/hour of water, respectively, at room temperature of 27°C and relative humidity of 25%.²¹ The same reduced significantly, in parallel with the clinical improvement of the skin at day 30, to 5.5 ± 2 g/m²/hour and 16 ± 2 g/m²/hour, respectively, at room temperature of 23°C and relative humidity of 37%.²¹

Metabolic Alterations

There is a raised BMR in patients with ASF, as explained above. About 50% of the patients demonstrate hyperglycemia, which may be multifactorial: stress, low insulin level due to pancreatitis, and relative insulin resistance.^{8,10} Hypophosphatemia is common in patients with wet disorders and augments insulin resistance.¹⁰ Protein depletion may occur to maintain the level of BMR, later manifested as muscle wasting. Overall, a catabolic state prevails.¹⁰

Alteration in Barrier Function

Both physical and immunologic barriers are at stake in patients with ASF. Loss of physical barrier, i.e., disruption of the stratum corneum, is the primary event, whereas loss of immunologic functions occurs secondarily. There is little evidence in the literature of local immunosuppression in patients with ASF in particular, but, such conclusion has been drawn from similar effects in patients with burn.⁸ There may be systemic immunosuppression in patients with TEN in the form of neutropenia (30%), total lymphopenia (90%), and selective CD4⁺ T lymphocytopenia.¹⁰ Granulocytic functions, e.g., chemotaxis and phagocytosis, are impaired.¹⁰ Altered immune functions make these patients prone to acquire infections.

Nutritional Loss

Loss of nutrients occurs through the damaged skin along with fluid and electrolytes. Normally, 500–1000 mg of material is lost per day through exfoliation, and this amount may increase

ninefold in patients with ASF. Diffuse scaling leads to protein loss of approximately 20–30 g/m² BSA/day.²² The blister fluid of autoimmune bullous disorders and TEN contains approximately 40 g/L of protein. In addition, protein is lost through oozing and hypercatabolism, accounting for total protein loss of 150–200 g/day.¹⁸ The associated hypercatabolism, fever, and sepsis increase protein metabolism and energy expenditure by 50%.²³ In pediatric patients with ichthyosis, the total calorie loss from daily TEWL ranges from 84–1015 kcal (21 ± 9.8 kcal/kg/day with a mean of 433 ± 272 kcal/day) to 41–132 kcal/day seen in age-matched children.²⁰

Dermatologic enteropathy leads to chronic diarrhea in patients with long-term erythroderma. Malabsorption of iron, vitamin B₁₂, and micronutrients occurs. Diarrhea also depletes the intestinal microflora resulting in deficiency of vitamin B complex. High cellular turnover in erythrodermic patients leads to folate deficiency.

ESTABLISHING THE UNDERLYING CAUSE

Establishing the underlying cause of ASF has two implications: first, obviously, making a complete diagnosis of an inpatient is obligatory, and second, it helps the clinician to administer definitive treatment during the recovery period of the patient; however, establishing the underlying illness giving rise to ASF in an admitted patient is a difficult task indeed! This is because most of the times at this point the patient is unable to give a

correct history and that obtained from the relatives may be incomplete and misleading. The responsibility falls upon the first clinician, who attends the patient in the emergency department, to elicit a plausible history, and to identify the clinical clues to the underlying cause. If few definite skin lesions (e.g., individual papule/vesicle) are identified, it is appropriate to perform simple bedside tests (e.g., Tzanck test, KOH mount from scales, etc.) and skin biopsy at this stage; otherwise, such investigations are postponed until the crisis period is over. Table 6.2 presents diagnostic clues for some of the underlying conditions in patients with ASF.

COMPLICATIONS

Complications of ASF are manifold. During the acute stage, there may be life-threatening complications arising mainly from hemodynamic alterations.¹⁰ Effects of this massive cutaneous injury leave cicatricial changes on skin, mucosa, and appendages; these are considered as “late complications.”¹⁰ Various complications of ASF have been presented in Table 6.3.

MANAGEMENT Hospitalization

All patients with ASF must be hospitalized, preferably in an intensive care unit (ICU). In some institutions, a facility for DICU is available, which meet the special needs of patients with ASF;

Table 6.2 Diagnostic Clues for Underlying Disorders in Patients with ASF

History/clinical features/investigations	Probable diagnostic interpretation
Scaly plaques, long-term scaling of scalp, nail changes	Psoriasis
Showers of pustular lesions with febrile episodes, lakes of pus	Pustular psoriasis
Spiny, follicular lesions, islands of normal skin between orange red erythema, palmoplantar keratoderma (PRP sandal)	Pityriasis rubra pilaris
Scaling since birth or soon after, H/O collodion membrane at birth	Congenital ichthyosis
H/O suggestive drug intake, icterus, hepatosplenomegaly, eosinophilia, elevated liver enzymes	Drug hypersensitivity syndrome
H/O drug intake, target lesions, mucosal involvement, hemorrhagic crusts on lip, positive Nikolsky sign	SJS-TEN
Poor hygiene, pruritus, mite demonstrable on light microscopy	Crusted scabies
Lymphadenopathy ± hepatosplenomegaly, bleeding episodes, abnormal peripheral blood smear	Lymphomas, leukemias
Greasy, scaly papular lesions in a neonate, hepatosplenomegaly, thrombocytopenia	Langerhans cell histiocytosis
Presence of bullae since/soon after birth, healing with scarring, milia formation, nail changes	Epidermolysis bullosa
Flaccid bullae, positive Nikolsky sign, positive Tzanck smear	Pemphigus

Table 6.3 Complications of ASF

Acute complications		Long-term complications	
Infection	Septicemia	Ocular	Ectropion, entropion, exposure keratitis, dry eyes (Figure 6.9), corneal ulcer, symblepharon (Figure 6.10)
Pulmonary	Acute respiratory distress syndrome (ARDS) Aspiration pneumonia Pulmonary embolism Pulmonary edema due to fluid overload	Esophageal	Stricture and dysphagia
Cardiovascular	High-output cardiac failure Congestive heart failure due to fluid overload Hypovolemic shock	Genital	Urethral meatal stricture, phimosis or vaginal stenosis (Figure 6.11)
Renal	Prerenal uremia Acute renal tubular necrosis	Cutaneous	Hypo- and hyperpigmentation, scarring
Gastrointestinal	Stress ulcers and gastric hemorrhage	Hair	Scarring alopecia
Neurological	Mental confusion and stupor resulting from electrolyte imbalance Meningitis spreading from septicemia	Nails	Beau lines, nail dystrophy, total shedding of nails (Figure 6.12)



Figure 6.9 Keratoconjunctivitis sicca following SJS.



Figure 6.10 Symblepharon in a patient following SJS.



Figure 6.11 Adhesion of labia minora causing vaginal stenosis as a sequelae of SJS.



Figure 6.12 Shedding of nails during convalescence period of SJS-TEN.

however, in the absence of such a facility, such patients may be admitted to a general ICU or even in a burn unit.

A multispecialty approach is required for appropriate care of patients with ASF. The basic team includes an internist or pediatrician, ophthalmologist, dietician, and dedicated nurses in addition to a dermatologist. Other specialists may be called upon as and when necessary.

Initial Clinical Evaluation

The first dermatologist attending a patient with ASF has the responsibility of assessing the hemodynamic status of the patient, to decide the immediate management protocol, and to initiate the treatment. An in-and-out history taking (recent and past) makes the job easier. The points and clinical parameters to be recorded at this stage are presented in Table 6.4.

TBSA involvement should be calculated.^{10,15} There are different methods of estimating BSA involved, used in patients with burn; *viz*, rule of nine, palm area of the patient, and Lund-Browder chart. The rule of nine is used for immediate assessment and it gives approximate values. This method should not be used in children less than 15 years of age.²⁵ With this technique, there is a tendency for overestimation of BSA involved, resulting in fluid overload, tissue edema, and subsequent pulmonary complications.²⁶ Similarly, use of palmar area is not accurate in patients with high body mass index (BMI). In these patients, it accounts for 0.64%, instead of 1% of BSA. A more accurate method is drawing the BSA involved on the Lund-Browder chart.²⁷

If a definitive diagnosis is possible, disease-specific indices are utilized to assess degree of involvement and prognosis (e.g., “psoriasis area severity index” [PASI] or “eczema area severity index” [EASI], etc.). In patients with TEN, a

Table 6.4 Initial Examination of a Patient with ASF²⁴

Record vital parameters	Pulse, blood pressure, respiratory rate, body temperature
Assess hydration	Hydration of tongue Skin turgidity
Level of consciousness	Conscious/unconscious If conscious, check orientation
Quick look all over skin, mucosa, hair, and nails	Search for clue to underlying disease Look for foci of infection
Any abnormal smell	May indicate secondary infection
General and systemic examination	Dependant edema, Pallor, Lymphadenopathy, Hepatosplenomegaly, Pulmonary congestion, Muscle weakness
Assessing risk factors	Old age Infants and children Pregnant women Patients with convulsive disorders Alcoholism, smoking habits
Assessing for comorbid conditions	Hypertension, diabetes mellitus, ischemic heart disease, chronic obstructive pulmonary disease Cirrhosis of liver, chronic kidney disease Tuberculosis, HIV infection

specific disease severity score, “SCORTEN,” must be assessed on admission and thereafter while monitoring.²⁴

Baseline Investigations

Judicious baseline investigations must be undertaken in all patients with ASF. A list of these investigations is presented in Box 6.2.

Setting Intravenous Channel

Setting an intravenous (IV) channel is the immediate action following admission to ICU. If the patient is critically ill, insertion of more than one canula may be necessary for hemodynamic monitoring and interventions. In all cases, the piercing should be done through relatively uninvolved skin as far as practicable to reduce the chances of introducing infection. If such an area of skin is not identifiable, setting a central venous line should be considered. The advantage of establishing vascular access immediately, even though the patient is not in critical condition, is manyfold; it enables the attending clinician to draw blood samples for multiple investigations, administer injectable

Box 6.2 Baseline Investigations in Patients with ASF

- Complete hemogram
- Blood glucose level
- Blood urea and creatinine
- Serum electrolytes (Na⁺, K⁺, Cl⁻, Ca⁺⁺)
- Serum HCO₃
- Liver function test
- Urinalysis
- Chest x-ray
- Electrocardiography (ECG)
- Arterial blood gas analysis

drugs, infuse IV fluids as and when indicated, and institute total parenteral nutrition (TPN).²⁸

Often in patients with severe SJS-TEN or extensive immunobullous diseases, where peripheral venous access in routine way or central venous catheterization is not possible, venesection should be considered.²⁸ The distal saphenous vein serves this purpose in an excellent way as it is easier to access due to consistent location, noncontiguity with important arteries and nerves, and distance from other resuscitative gadgets.²⁸

Urinary Catheterization

An accurate calculation and maintenance of the intake/output (I/O) chart is vital for patients with ASF. In bedridden patients transurethral catheterization or condom drainage (male patients) is an absolute necessity for this purpose.²⁸ The risk of introducing urinary tract infection during catheterization can be minimized by condom drainage (Texas catheter); however, this method is not possible to adopt in cases with damaged penile skin. In neonates and pediatric patients, neonatal and pediatric “urine collectors” may be used for collection of urine.²⁸ In ambulant patients, urine can be collected in graduated bottles and the record is kept.

Nasogastric Intubation

Any patient with ASF due to any cause should be encouraged to take fluids and food orally as far as possible; however, this may be difficult for patients with SJS-TEN and pemphigus due to painful oropharyngeal and esophageal erosions. Insertion of a nasogastric tube is helpful in such cases. All acutely ill patients with ASF unable to take orally should have a nasogastric tube inserted. Various advantages of nasogastric intubation in patients with ASF are presented in Box 6.3.

Following insertion, the correct location of the tube must be double-checked to prevent accidental aspiration.²⁸ The clinician must undertake due precaution to insert a nasogastric tube in conditions with fragile mucosa to avoid the risk of traumatic hemorrhage and esophageal perforation.²⁸

A schedule for Ryle tube feeding must be prepared by the clinician, dietician, and on-duty nursing staff. The total amount is divided into small feeds (one fourth of the desired amount) and administered at regular intervals as overfeeding may lead to regurgitation and aspiration.²⁴

While recovering, nasogastric feeding is gradually substituted by oral intake (liquid or semisolid) and as the condition permits, full oral diet is instituted.²⁴

Use of Air-Fluidized Bed

The purpose of using these devices in patients with ASF is prevention of pressure sores. Water beds are made up of soft

Box 6.3 Various Usage of Nasogastric Tube in Patients with ASF²⁸

- Feeding
- Administration of oral medications
- Periodic aspiration of gastric contents
- Detection of stress-induced gastrointestinal bleeding
- Management of gastric immobility and paralytic ileus in acutely ill patients

polyvinyl chloride (PVC) or similar material and are provided with single or interconnected flow chambers to fill it with water.²⁹ Air-fluidized beds have interconnected air and fluid chambers. The water may be warmed with a thermostatic device connected to the bed.²⁹

During use, an air-fluidized bed is shaped around the patient's body and thus reduces contact time and pressure, especially over bony prominences.²⁹ It may be set at body temperature or according to the patient's comfort level²⁹; however, a water bed with a temperature regulation system may result in dysregulation of body temperature and dehydration in patients with ASF.²⁹ A floating sensation may make some patients feel uncomfortable.²⁹ The caregivers should be alert to accidental leakage from the bed.²⁹

Maintenance of Body Temperature

Patients with ASF are at risk for developing hypothermia. At environmental temperature, it is invariably associated with shivering and loss of extra calories. This precipitates a hypercatabolic state and negative energy balance. An optimum room temperature (30–32°C)¹⁰ has to be maintained for these patients to avoid such consequences, and this can be achieved by air-conditioning. At presentation, hyperthermia in some patients as discussed before should be taken into consideration before a final decision is made regarding regulating environmental temperature.¹⁰

Maintenance of Fluid and Electrolyte Balance

In a state of ASF, depending on the underlying cause and severity, significant amounts of fluid and electrolytes are lost through the skin resulting in serious hemodynamic consequences. The use of drugs in a hemodynamically unstable patient of ASF to the patient's benefit has been inconsistent; hence, the successful management of these patients mainly depends on maintenance of fluid and electrolyte balance in addition to other supportive therapies. Adequate fluid resuscitation is based on the knowledge of

- Fluid and electrolyte balance
- Accurate estimation of BSA involved
- Volume and nature of fluid lost
- Comorbid conditions and clinical scenarios that may worsen the existing condition and/or act as risk factors for development of complications related to fluid resuscitation

There is a dearth of studies on estimation of fluid and electrolyte loss and their management in ASF; therefore, extrapolation of the guidelines used for management of fluid and electrolytes in burn patients and other critically ill patients is recommended for patients with TEN and other patients with ASF.

Assessment of BSA Involved

Accurate assessment of BSA involved in patients with ASF is essential for calculation of adequate resuscitation fluid and better patient outcome.

Estimation of Replacement of Deficit Fluid

Replacement of fluid that is already lost should be provided during the first 24 hours after injury. It is essential for maintenance of tissue perfusion, blood pressure, and adequate urine output.

Estimation of Replacement Fluid in TEN

The Parkland formula²⁵ is used to calculate the replacement fluid, because the injury that occurs in TEN is comparable to burns. The Parkland formula is as follows:

$$\text{Resuscitation volume} = 4 \text{ mL} \times \text{Total body weight} \times \% \text{ of epidermolytic BSA involved}$$

In TEN, the epidermal denudation occurs at the level of dermoepidermal junction like superficial burns.^{12,23} In addition, the absence of the thermal effect, moderate papillary edema, and normal reticular dermis make patients with TEN less susceptible to fluid and electrolyte loss when compared to burns covering the same BSA.^{30,31} Even in burns with involvement of large BSA and in patients with high BMI, the Parkland formula overestimates the volume of replacement fluid required during the first 24 hours²⁷; hence, aggressive fluid resuscitation is not required in patients with TEN.³² One half to three-quarters of the resuscitation volume calculated by the Parkland formula is recommended during the first 24 hours after injury.^{18,33}

Estimation of Water Deficit in Erythroderma

Unlike TEN, in patients with erythroderma the TEWL is solute free. The water deficit is calculated here based on plasma Na⁺ levels, as follows:

$$\text{Water deficit} = \frac{\text{Plasma Na}^+ \text{ concentration} - 140}{140} \times \text{Total body water}$$

In hyponatremia total body water is 50% and 40% of lean body weight in men and women, respectively.¹¹

Estimation of Maintenance Fluid and Ongoing Evaporative Loss

After administration of replacement fluid during the first 24 hours, the maintenance fluid and additional fluid to compensate for ongoing loss (through the damaged skin) should be provided. Maintenance fluid is designed to supply free water and electrolyte requirements in a fasting patient. The requirement of free water in a healthy child is equated with that of energy expenditure; hence, the maintenance fluid is calculated as follows:

100 mL/kg/day for first 10 kg (1000 mL), 50 mL/kg/day for next 10 kg (1000 mL + 500 mL), and 20 mL/kg/day above 20 kg (1500 mL + 20 mL/kg).³⁴

If urine output is low and is not improving, then the volume of maintenance fluid should be reduced to 50%.¹²

The evaporative loss of fluid is calculated by using the following formulas:

- Insensible water loss = (125 + % TBSA involved) × TBSA (m²)³⁵
- Evaporative water loss (through eroded skin in children) = 25 + % TBSA involved × TBSA (m²)²³

Choice of Fluid for Replacement Therapy

Various factors like age, severity of disease, and underlying metabolic changes determine the choice and rate of administration of IV fluid during replacement therapy. Generally, oral administration of fluids is preferred over IV fluids. IV fluids are recommended if TBSA involvement is >10% in children and >15% in adults. If the patient is not in severe shock, oral fluids can be started within 24 hours providing one quarter of the daily fluid requirement. As the condition of the patient improves slowly, IV fluid is replaced with oral fluids.²⁵ Table 6.5 presents the composition of various resuscitation fluids and advantages and disadvantages of their usage.

Choice of Fluid in TEN

The replacement fluid calculated by the Parkland formula is based on crystalloids. Usually isotonic solutions like Ringer lactate (RL) and 0.9% normal saline (NS) are recommended for replacement therapy. The choice of fluid for immediate restoration of intravascular volume is RL. Half of the calculated volume is administered in the first 8 hours and the remaining half in the subsequent 16 hours²⁵; however, depending on the severity of volume depletion, the replacement fluid can be administered in 8–12 hours.³⁶ NS can be used especially in infants and young children who are predisposed to lactic acidosis and hyponatremia.¹⁵

If TBSA involved is >40%, IV colloidal resuscitation with 5% human albumin in NS is recommended due to the hypercatabolic state and movement of protein into the extravascular space, which results in a significant amount of protein loss^{23,25}; however, it is not recommended during the first 24 hours due to

the presence of a significant capillary leak. The dosage of albumin is calculated as $0.3\text{--}0.4\text{ mL/kg} \times \% \text{ of BSA involved}$, to be administered over 6–8 hours.³⁷

Choice of Fluid in Erythroderma

In hypernatremic dehydration, restoration of intravascular volume is achieved by infusion of 10–20 mL/kg/hour of RL or NS in 1–2 hours before replacement of water deficit. In premature and small infants, NS is preferred.³⁴ Once the intravascular volume is restored, half of the calculated water deficit should be replaced during the first 12–24 hours and the remaining over 48–72 hours by using isotonic NS.³⁸

Choice of Fluid for Maintenance Therapy

In the hypovolemic state, nonosmotic secretion of antidiuretic hormone (ADH) results in avid water resorption by kidneys and reduced urine volume. In such a situation, administration of hypotonic solution, which has been followed traditionally, may put the patient at risk of hyponatremia; hence, an isotonic solution like NS is recommended for maintenance fluid therapy.³⁹ The evaporative loss is replaced preferably with free water; however, 5% dextrose in 0.2% saline is used to prevent water intoxication and electrolyte imbalance.²³

Monitoring of Fluid and Electrolyte Therapy

The formulas used for estimation of volume in the treatment of patients with ASF give only rough guidelines for fluid therapy due to various reasons described above. The cornerstone of successful fluid resuscitation is careful and continuous monitoring of clinical and laboratory parameters. Though mean

Table 6.5 Composition of Various Resuscitation Fluids and Their Usage²⁴

Type of fluid	Comments	Type of fluid	Comments
Colloids	More effective in expanding intravascular volume, by maintaining colloid oncotic pressure. Volume sparing effect is an added advantage (Colloid: crystalloid = 1:3).	Crystalloids	Inexpensive, widely available, established role as first-line resuscitation fluid. Risk of significant interstitial edema.
A. Natural			
1. Human albumin (4%–5%) in saline	Reference colloid solution Ideal IV fluid in early sepsis Limiting factors: high cost, limited availability in resource-poor setup	1. Normal saline (0.9%) (NS)	Most commonly used crystalloid solution. Large volume transfusion results in hyperchloremic metabolic acidosis, acute renal injury.
B. Semisynthetic colloids	Shorter duration of action than albumin, but actively metabolized, and excreted	2. Hartman/Ringer lactate	Contains K ⁺ (5.4 mmol/L), Ca ⁺⁺ (2 mmol/L) and lactate (29 mmol/L); advantageous over NS when supplementation required.
1. Hydroxyethyl starch	Colloid source is potato or maize starch. Recommended maximum daily dose 33–50 mL/kg/day. Contains K ⁺ , Ca ⁺⁺ , Mg ⁺⁺ , lactate, and malate in addition to Na ⁺ and Cl ⁻ , depending on the brand. Adverse events: pruritus, altered coagulation, acute kidney injury, and increased death rate	3. Balanced salt solution	Considered as initial resuscitation fluid. Chemical composition approximates ECF. Relatively hypotonic due to lower sodium concentration. Nonbicarbonate anions, like lactate, gluconate, acetate, and malate, are used. Excess use: risk of hyperlactatemia, metabolic alkalosis, hypotonicity, and cardiotoxicity. Some brands contain calcium and have the risk of microthrombi formation with citrate containing red cell transfusion.
2. Dextran	Infrequently used.		
3. Succinylated modified fluid gelatin (4%) and urea-linked gelatin (3.5%) (Hemacel)	Colloid source is bovine gelatin. Hemacel contains K ⁺ (5.1 mmol/L) and Ca ⁺⁺ (6.25 mmol/L)		

Box 6.4 Monitoring Fluid Transfusion Based on Urine Output

- Urine output equal to or less than one third of predicted value over 2 consecutive hours: Rate of IV fluid infusion increased by 20%/hour.
- Urine output more than predicted value: Rate of IV fluid infusion decreased by 20%/hour.³⁵

Other recommendation²⁵:

- Urine output <1 mL/kg/hour: Increase IV fluid infusion by 50%.
- Urine output >2mL/kg/hour: Decrease the rate of infusion.

arterial pressure, central venous pressure, and central venous oxygen saturation are the accurate indicators of hemodynamic response to fluid therapy, in patients with ASF invasive monitoring techniques are not recommended to avoid the risk of sepsis.^{15,39}

The main goal of fluid resuscitation is maintenance of normal urine output (0.5–1.0 mL/kg/hour), blood pressure, heart rate, and serum Na⁺. In children, capillary filling time is measured to assess the response to fluid resuscitation. Based on urine output, monitoring of fluid infusion is presented in Box 6.4.

The clinical signs and symptoms suggestive of dehydration and electrolyte imbalance (Table 6.6) should be monitored frequently. A pulse rate of ≥ 120 in a patient with ASF may be indicative of negative fluid balance, even in the presence of other factors like fever and septicemia; the recording of blood pressure in these patients may be misleading as it tends to remain normal in the initial stage.¹⁰

During treatment of hyponatremia, rapid correction of plasma Na⁺ by 1–2 mEq/L/hour should be limited to the initial phase of management. Later, to prevent osmotic demyelination, the correction of plasma Na⁺ levels should not exceed 8–12 mEq/L in 24 hours.

Patients with erythroderma are more prone to develop severe hypernatremic dehydration due to solute free water loss. In such a situation, water enters the cells during rehydration leading to intracellular edema; hence, the fluids should be

administered very slowly to prevent brain cell injury. The serum sodium should fall by 0.4–0.8 mEq/L/hour or 10–12 mEq/L/day, and the maximum rate of fall in plasma Na⁺ should not exceed 2 mEq/L/hour.³⁸

Nutritional Supplementation in ASF

The main goal of nutritional therapy is to supplement the catabolized proteins, provide proteins required for healing of skin lesions, and ensure growth in case of children.¹⁵ Adults with >15% and children with >10% of BSA involved have an increased nutritional requirement;²⁵ therefore, aggressive nutritional supplementation should be started preferably through the enteral route.

Enteral feeding has the advantage of preserving gastrointestinal integrity and decreasing the incidence of bacterial transmigration across the gut, but complications pertaining to insertion of the nasogastric tube have already been discussed. TPN is also associated with complications related to IV line insertion, sepsis, and metabolic risk.⁴⁰ Delivery of nutrition without using nasogastric tube or central venous line has been proposed. It is done in two phases, initially low osmolality TPN is administered through peripheral veins followed by oral supplementation of nutrition as soon as the clinical condition permits.⁴¹

If the patient is not toxic and gastrointestinal functions are intact, the feeding can be started within 6 hours of injury.²⁵ In children with burns involving <20% of BSA, the gastrointestinal motility returns to normal in 72 hours, and in extensive involvement, paralytic ileus may persist for 5–6 days.³⁷ In such patients with impaired gastric emptying, enteral feeding is initially started with one quarter of the desired volume and is gradually increased at a rate of 5 mL/hour. The residual gastric volume should be checked by periodic aspiration and feeding is stopped if it is more than 50 mL.¹⁵

As in fluid and electrolyte therapy, various formulas used for calculation of protein and energy requirements in burns can be extrapolated for TEN. The calorie requirement of pediatric patients with TEN was found to be 22% less per day than those with burns. A formula has been developed as follows⁴²:

$$\text{Calorie requirement} = \text{Baseline body weight (Kg)} \times 24.6 + \text{Wound size (\%TBSA)} \times 4.1 + 940$$

Table 6.6 Signs and Symptoms Suggestive of Dehydration and Electrolyte Imbalance

Age Group	Dehydration	Electrolyte Imbalance
Children and infants ³⁴	Mild: 3%–5% loss of body weight, reduced urine volume, minimal clinical sign Moderate: 6%–10% loss of body weight, tenting of skin, lethargy and sunken eyes Severe: 11%–15% loss of body weight, hypotension, tachypnea, tachycardia, oliguria, and altered sensorium Note: In hyponatremia, degree of dehydration is less and in hypernatremia degree of dehydration is more than clinical features suggest. ³⁶	<ul style="list-style-type: none"> • Hyponatremia Muscle weakness, dizziness, hypotension, and tachycardia³⁹ (Symptoms uncommon if plasma Na⁺ is >120–125 mmol/L) Rapid fall in plasma Na⁺ to <125 mmol/L results in appearance of symptoms, and to <110 mmol/L causes seizures and coma • Risk factors for osmotic demyelination:³⁸ Alcoholics, malnourished, hypokalemia, elderly women on thiazide diuretics, and patients with plasma Na⁺ <105 mEq/L • Hypernatremia Restlessness, irritability, lethargy, confusion, and somnolence
Adults	Dry tongue and mucosae Loss of skin turgidity Intense thirst Confusion and somnolence Hypovolemic shock	

Protein requirement is calculated by Davies formula, as follows:²⁵

Children : 3 g / kg + 1 g / % BSA involved

Adults : 1 g / kg + 3 g / % BSA involved

Isodense formulas that give 100 kcal/100 mL are preferred and are well tolerated. Based on the caloric value of food articles like milk (100 mL = 60 kcal), sugar (1 tsp = 20 kcal), and cereals (1½ tsp = 20 kcal), various isodense kitchen-based enteral feeds are prepared, as enumerated below:

- | | |
|---------------------|---|
| 1. High energy milk | 100 mL milk + 1 tsp sugar + 1/2 tsp oil |
| 2. Cereal milk | 100 mL milk + 1 tsp sugar + 1½ tsp cereal flour |
| 3. Fruit juice | 1 orange + 2 tsp sugar + water up to 100 mL |
| 4. Egg flip | 1 egg + 2 tsp sugar + 150 mL milk |

Commercially available enteral preparations can also be used.⁴³ In addition to protein and energy, daily supplements of vitamins, minerals, and trace elements are provided.²³

Immune modulating parenteral nutrition containing glutamine, arginine, and omega-3-fatty acids has been demonstrated to benefit the patients with TEN. The immune modulating approach has been used successfully in burn and other critically ill patients. Glutamine acts as oxidative fuel for lymphocytes and mucosal cells; arginine promotes lymphocyte maturation and activation; and omega-3-fatty acids lead to decreased production of proinflammatory mediators; thus, these substrates benefit the patients with critical illness by reducing infections, requirement for ventilator, and length of stay.⁴⁴

Prevention of Infection

Superadded infections are common in patients with ASF. These worsen the existing skin disease and enhance chance of septicemia. During hospitalization of a patient with ASF, the attending dermatologist must look for focus of skin infections, like folliculitis, abscess, infected fissures, chronic suppurative otitis media, tooth abscess, etc. History of fever in the past few days may indicate underlying systemic infection. The presence of tachypnea may indicate underlying pneumonia.¹⁰

Patients with ASF are always at risk of septicemia and septicemic shock. Even in frank septicemia, patients may remain afebrile or even hypothermic causing dilemma in diagnosis. Two subtle signs of septicemic shock are reduction in urine volume and altered sensorium, which should be detected at the earliest possible time.¹⁰

Even in the absence of frank infection on admission, a culture sensitivity test from skin should be sent for all patients of ASF routinely. This will help in the selection of antimicrobials, if required in the future. If initial skin culture is negative, a repeated skin culture sensitivity test should be sent weekly during the patient's hospital stay, for early detection of nosocomial infection. In a febrile patient with ASF, blood culture and urine culture are part of the diagnostic panels.

Barrier nursing must be practiced stringently. Daily sponging and cleaning of body orifices, like oral cavity, nostrils,

external auditory canal, genitalia, as well as teeth and gums, eyes, perineum and perianal area must be undertaken. Any pus collection must be drained.

As soon as the patient's condition improves, a gentle bath in lukewarm water with antibacterial soap should be started. During the cleaning process, all debris, dead skin, discharge, and crusts are removed, preferably following lubrication with liquid paraffin.

Antimicrobials should be started in the presence of cutaneous and systemic infection, initially empirically and thereafter based on culture sensitivity report. Caution should be taken in patients with DHS or drug-induced SJS-TEN to avoid accidental use of the same group of drug.

Skin Care

In patients with ASF due to "wet disorders," the skin is tender and bleeds easily. Gentle handling is recommended for them to avoid further damage to the skin. This is especially true for neonates with epidermolysis bullosa, where trauma may precipitate new lesions. Patients should be laid on a non-adherent McIntosh sheet, spread over the bed. Loose clothing without any elastic bands is preferred. Adhesive tape is avoided and resuscitative gadgets should be fixed with roller bandage instead. An air-fluidized bed or frequent posture change is recommended to avoid the formation of pressure ulcers.

Intact bullae should be incised to drain the fluid and the roof is allowed to rest on the floor so that it acts as a biological covering. Raw areas of skin are covered with sheets of lubricated (white soft or liquid paraffin) gauze, changing every day. Various biological dressings are available, which can be used depending on availability.

The skin of patients with erythroderma (dry disorders) often develops deep, painful fissures. These can be managed with lubricants and topical antimicrobials.

Ocular Care

Sight-threatening ocular involvement can occur in SJS-TEN and long-term erythroderma. In patients with SJS-TEN, conjunctival adhesions are separated with a clean glass rod several times a day to prevent synechiae formation. Ectropion and exposure keratitis are the sequelae of long-term erythroderma. Ectropion is managed with instillation of artificial tears at periodic intervals and eye-pads at bedtime. In the presence of exposure keratitis, gas-permeable scleral contact lenses may be used to reduce photophobia and discomfort.¹⁰

Genital Care

In "wet disorders" with ASF, there is risk of adhesions on opposing denuded surfaces of male and female genitalia. The sequelae are phimosis in men and vaginal stenosis in women. Genitalia of these patients must be inspected and cleaned daily, and adhesions must be broken gently with a glass rod at the earliest. Placing a sterile wet gauze piece between prepuce and glans penis in men and a wet swab between the walls of the vagina in women prevents adhesions.

Therapeutic Intervention

Therapeutic interventions may be "supportive" or "disease specific." Medications must be used very judiciously in patients with ASF, especially when the underlying cause is

Table 6.7 Indications of Supportive Therapy in Patients with ASF

Indications		
Prophylactic administration	Administration on indication	Drugs administered
Prevention of stress ulcer	Evidence of frank infection (cutaneous/systemic)	H2-blockers/proton-pump inhibitors Antimicrobials based on culture sensitivity report
Prevention of stress	Anxious patient Disturbing pruritus SJS-TEN Hyperglycemia	Short-acting benzodiazepine (Alprazolam) at bedtime Antihistamines Short course of systemic steroid to reduce inflammation Intensive insulin therapy ⁸
Prevention of nutritional deficiency		Supplementation of the following: <ul style="list-style-type: none"> • Vitamin B complex • Vitamin D • Vitamin C • Iron • Commercially available protein powder mixed with milk

Box 6.5 Indications of Antibiotic Use in Patients with ASF

1. Isolation of single-strain bacteria (high colony count) from skin specimen/catheter sample of urine
2. Sudden hypothermia in a relatively stable patient (septicemia)
3. Sudden confusion/delirium (meningitis)
4. Pneumonia
5. Urinary tract infection

Table 6.8 Disease-Specific Therapy in Patients with ASF

Conditions	Treatment
Psoriasis	Methotrexate, cyclosporine, phototherapy
Dermatitis	Systemic corticosteroids, cyclosporine, azathioprine
Ichthyosis	Systemic retinoids
Immunobullous disorders	Systemic corticosteroids, adjuvant immunosuppressive drugs
Dermatophyte infection	Systemic antifungals; terbinafine, itraconazole
Crusted scabies	Repeated topical application of permethrin (5%) + oral ivermectin
SSSS	Antistaphylococcal antibiotics; cloxacillin, linezolid
SJS-TEN	Systemic steroid, intravenous immunoglobulin G
DHS	High-dose systemic steroid tapered slowly over a period of time

drug-induced reactions; however, often it is crucial to administer drugs as supportive therapy, but the indications must be genuine and close supervision is mandatory. Some drugs are administered prophylactically, whereas others only when indicated. Various indications of supportive therapy in these patients are presented in Table 6.7.

The relevance of the use of systemic antimicrobials in patients with ASF is controversial and should be used only when indicated, as presented in Box 6.5.

Disease-specific therapy can be started initially when a tentative underlying cause has already been identified or subsequently when the diagnosis is established. A list of these drugs is presented in Table 6.8.

PROGNOSTIC FACTORS IN ASF

Poor prognostic factors in a patient with ASF on admission are extremes of age, high TBSA involvement, the presence of cytopenias (neutropenia, thrombocytopenia), chronic kidney disease, and other comorbid conditions (hypertension, diabetes, obesity/malnutrition, tuberculosis, HIV infection). In drug-induced cases, if the precipitating drug has a long half-life, it confers a poorer prognosis.¹⁰

While under treatment in the ICU, development of any of the acute complications as described in Table 6.3 carries poor prognosis. These are associated with risk of mortality in patients with ASF.

CONCLUSIONS

Irvine's concept of "acute skin failure" has proven to be a real entity. Awareness and discussion on this subject in dermatologic meetings have gained momentum in recent years; however, proper research work involving patients with ASF is still sparse in the dermatology literature, and a "burn model" is being used for pointing out therapeutic strategies for these patients. DICU is available in limited institutions, and the concept of ASF, among other medical and paramedical fraternities, is still vague. Dermatologists will have to work still harder to establish the concept of ASF for the benefit of these patients.

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Dermatologic emergencies in neonatal medicine

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Numerous skin lesions can be seen in a newborn,^{1,2} even in the setting of neonatal intensive care units (NICUs),³ and the majority require an urgent diagnosis. The purpose of the clinical workup is to suspect an infection, which must be treated on a presumptive basis, or to diagnose a noninfectious dermatosis. Some of these neonatal dermatoses are of clinical significance and various severity, others are benign and transient. In this latter case, a diagnosis is urgent to spare useless investigations and therapy, and to reassure the parents.

PREMATURITY AS A CUTANEOUS EMERGENCY

The main function of the skin is to constitute an interface, called a barrier, between the organism and the environment. This barrier controls water, electrolytes, and heat losses, and the penetration of noxious agents. The skin is also an antiinfectious barrier, and the commensal flora established since birth participates in this immune surveillance. This barrier function relies on the integrity of the stratum corneum, which is formed during the last trimester of gestation. It begins to develop at approximately 24 weeks and a structured stratum corneum becomes evident between 32 and 34 weeks. The complete maturation, however, may take 8–10 weeks after birth. So in premature newborns, the stratum corneum is immature and inefficient. Its permeability is greatly increased and it is also more fragile toward physical trauma (including adhesives and other medical devices).

Babies born before the 37th gestational week lack an efficient epidermal barrier and are at risk of dehydration, hypothermia, infection, mechanical trauma, and systemic toxicity of topicals. Premature newborns must so be considered as suffering from a cutaneous insufficiency, and immediate measures must be taken to avoid rapid death. The same is true of term newborns with extensive skin lesions. The procedures of neonatal medicine, including the care in heat- and hydration-controlled incubators, aim at alleviating the consequences of this cutaneous insufficiency.⁴

Principles of Care of Premature Babies

To prevent excessive water losses, hypothermia, dehydration, and their metabolic and hemodynamic consequences, premature newborns are put in a plastic bag as soon as they are taken care of after birth. In NICUs, they are placed in double-walled incubators with automated control of temperature and humidity. The relative humidity is kept between 70% and 90% during the first 2 weeks of life. Fluid replacement is adjusted. It is a pragmatic habit to apply vegetal oil on the skin. Pressure sores must be actively prevented.

The immaturity of the skin barrier and of hepatic and renal epuration processes, as well as the elevated surface/weight ratio, result in a high risk of systemic toxicity from

percutaneous absorption. There have been many reports of toxic effects of drugs or nondrug topicals, mainly antiseptics.⁵ All chemicals applied on a baby's skin may be absorbed. Such systemic poisoning must be prevented, especially in premature babies, in babies with diseased skin, and on the skin covered by diapers. All potentially harmful substances must be avoided, in drugs and in hygiene and skin care products.

Prevention of Cutaneous Trauma from Neonatal Intensive Care

Monitoring and therapy of newborns in NICUs require the use of many devices that can harm the skin: probes for blood gas analysis, cardiograms, temperature monitoring, and so on, may cause irritations and burns. Simple adhesives used to fix infusions, tubes, and probes induce erosions and a profound alteration of the barrier function. The greatest care is needed from all professionals to minimize all these iatrogenic traumas, maintain skin integrity, and prevent infections.⁶

EMERGENCIES IN NEWBORNS WITH SKIN LESIONS

The clinical morphology of the skin lesions is a valuable guide to help the neonatologist diagnose neonatal dermatoses. In this overview of neonatal emergencies, we insist on the constant preoccupation of an early suspicion, diagnosis, and treatment of life-threatening infections.

A NEWBORN WITH BLISTERS An Emergency: Rule Out a Staphylococcal Infection

Staphylococcal infections are frequent in newborns in NICUs. They usually result from a postnatal contamination. The presence of invading devices increases the risk of cutaneous and systemic infections: ventilation tubes, intravenous catheters, and nasal ventilation devices.

Coagulase-negative staphylococci (CoNS), a normal component of the skin microbiome, colonize the skin from birth. Systemic penetration of cutaneous CoNS is one of the major causes of neonatal sepsis.⁷ Cutaneous lesions are poorly recognized; pustules may be secondary to CoNS infection. Prognosis is good due to the efficacy of antibiotics.

Staphylococcus aureus is the major cause of acquired blistering eruptions in the newborn. Newborns are exquisitely sensitive to the infection by exfoliatin-producing *Staphylococcus aureus* strains, due to the immaturity of the epidermal barrier and of the renal elimination of toxins.

S. aureus infections are acquired postnatally and must be prevented by adequate hygiene and antisepsis of the nurseries,

including the mothers, family members, and health-care workers. General hygiene of the facilities, “surgical” hand washing, meticulous care of the nipple area of feeding mothers, and non-toxic antiseptic care of the umbilicus (aqueous chlorhexidine) are a mandatory part of this prevention.

Staphylococcal blisters are induced by some strains of phage group II *S. aureus*.⁸ The portal of entry is a superficial infection: cutaneous wound (umbilicus, circumcision, puncture, diaper rash, heel prick), nasopharynx, conjunctiva. It shows yellow crusts, erythema, and oozing, small pustules.

Epidermolytic toxins are disseminated through the bloodstream and exert a proteolytic activity on desmoglein 1, leading to an exfoliation at the subcorneal level of the epidermis.

Bullous impetigo is the localized form of the staphylococcal toxic bullous disease. Lesions appear as flat, flaccid bullae, rapidly ruptured, leaving round erosions or crusts (Figure 7.1). If untreated, these localized infections may lead to several types of complications:

- Cellulitis, fasciitis, abscesses, lymphadenitis
- Osteomyelitis, arthritis, septic pleuritis, pneumonia, septicemia, by hematogenous spread
- A toxic generalized skin disease called SSSS (staphylococcal scalded skin syndrome)

SSSS⁹ begins as a bright, scarlatiniform, erythematous rash, predominating in periflexural and periorificial areas. Rapidly, the superficial part of the epidermis is shed, with extensive peeling, or superficial blistering, and a positive Nikolsky sign (Figure 7.2). This desquamation phase lasts 2 to 4 days and is followed by complete healing, without scarring.

Complications may include dehydration, hypothermia, and generalized sepsis.

Differential diagnosis includes all neonatal bullous eruptions. The onset after a few days helps in differentiating infectious blisters from epidermolysis bullosa.

SSSS is extremely rare in low birth weight newborns, but it may be a very severe and fatal disease. In other cases, the prognosis is good, provided adequate measures are taken:



Figure 7.1 Widespread staphylococcal impetigo.



Figure 7.2 Staphylococcal scalded skin syndrome (SSSS).

- Intravenous antimicrobials
- Isolation in an incubator
- Nontraumatic skin care, including the use of emollients (sterile petrolatum, paraffin oil); the shedding epidermis must be conserved as a “biologic dressing”

Other Neonatal Bullous Eruptions

Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a group of rare genetic diseases, characterized by an increased fragility to mechanical trauma (mechanobullous diseases), resulting in an epidermal detachment. There are many EB subtypes of variable severity, including severe, lethal, or incapacitating forms. Each of these subtypes is due to a genetic defect in one of the many molecules involved in the cohesion between the epidermis and the dermis. They are classified by mode of inheritance, clinical features, histopathology, and molecular defect.¹⁰

The Newborn with Epidermolysis Bullosa

The birth of a child with EB is a difficult problem that is better dealt with within a NICU, in cooperation with a reference center.

Trauma- or friction-induced blisters are the hallmark of EB. These blisters are initially located on the areas of presentation in case of vaginal delivery and are induced through handling by the obstetrician, midwife, and neonatal staff. Some areas may appear to be devoid of skin (Figure 7.3).

The child must be placed in an incubator, while it is important to avoid overheating, and the general principles of



Figure 7.3 Skin detachment, appearing as an absence of skin, in a newborn with recessive dystrophic epidermolysis bullosa.

care are similar to those for very premature infants, whose skin is also fragile.

A skin biopsy will be very helpful in establishing a precise diagnosis. The biopsy must be taken on a normal appearing, recently rubbed area to induce splitting. In addition to conventional histology, antigen mapping (laminin 332, collagen VII), performed in a specialized pathology laboratory, will allow a subtype diagnosis, which is important both for the patient and for future prenatal diagnosis.¹¹ DNA mutations may be identified in the blood cells of the child and his or her parents.

The Main Epidermolysis Bullosa Subtypes

Epidermolysis Bullosa Simplex The most common EB type, called the Koebner type, is an autosomal dominant, relatively mild disease. It is due to mutations of keratins 5 and 14. The bullae are intraepidermal and heal without scarring. Even in the case of neonatal onset, nails and mucosae are uninvolved, there is no extracutaneous manifestation, and the prognosis is good with progressive improvement.

Junctional Epidermolysis Bullosa The Herlitz type of junctional EB is a rare, very severe, often lethal disease. It is an autosomal recessive disorder, due to mutations of laminin 332, which induce splitting at the level of the lamina lucida. Since birth, bullae and large erosive areas heal very slowly (Figure 7.4). The formation of granulating tissue following blisters around the nails is characteristic. There is a severe mucosal involvement, with oral blisters, respiratory, digestive, urinary lesions, and ocular complications. Failure to thrive, anemia, and later severe dental problems cause many distressing and life-threatening local and systemic complications. Patients with Herlitz disease die early in childhood.

Dystrophic Epidermolysis Bullosa Dystrophic EB is due to mutations of the *COL7A1* gene, coding for collagen VII, a major component of anchoring fibrils. Blisters in the superficial dermis heal poorly, with scars and many complications.

Recessive dystrophic EB (Hallopeau-Siemens type) is a severe disease. Extensive blistering since birth leads to



Figure 7.4 Superficial ulceration in junctional epidermolysis bullosa.

large, nonhealing ulcerations, atrophic scars, and joint contractures. On the hands and feet, repeated blistering and abnormal scarring end in a “mitten-like” deformation, functional limitation, and severe handicap. Oral ulcerations and digestive involvement are frequent. Children face multiple nutritional deficiencies, growth failure, ocular and urinary complications, and high susceptibility to infection (and later to squamous cell carcinomas). The management of a child with recessive dystrophic EB requires a trained specialized multidisciplinary team.

Principles of Management of a Newborn with EB

No therapy is currently able to correct the skin fragility. Trials of cellular therapy have been recently performed.¹² In severe forms, general medical and psychologic support are most important. Reference centers and specialized associations exist in many countries.

The main principles of the management of a newborn with EB are¹³ special attention for the avoidance of all trauma to the skin, use of bland emollients, nonadhesive dressings, protection of all fragile areas, feeding with special bottles in case of oral lesions, and attention to all the numerous possible complications, including pain, bacterial infection, dehydration, and undernutrition.



Figure 7.5 Neonatal syphilis. (Courtesy of Odile Enjolras, MD.)

Neonatal Syphilis

Congenital syphilis has nearly disappeared in countries where serologic screening is performed in pregnant women. It is important to know, however, that there has recently been a reemergence of syphilis. In high-risk women, a serologic control at the end of pregnancy is recommended. The treatment of infected women is an efficient prophylaxis for neonatal syphilis.

The first sign of congenital syphilis is rhinitis, a very unusual sign in newborns. Many types of cutaneous eruptions may be seen, including a characteristic bullous eruption of the palms and soles (Figure 7.5). Congenital syphilis is a systemic infection with hepatic, bone, and neurologic manifestations. Spirochetes can be found in the lesions. Serologic tests are reactive, particularly the FTA-ABS IgM (fluorescent treponemal absorption IgM). Parenteral penicillin G is the first-line treatment.

Porphyrria

Congenital erythropoietic porphyria, or Gunther disease, is due to the absence of uroporphyrinogen III synthase. Children suffer from extreme photosensitivity, which may induce blistering on exposed areas, and skin fragility, beginning in the neonatal period.

Autoimmune Bullous Diseases

Transient neonatal blistering may be caused by the transplacental transmission of maternal autoantibodies. The diagnosis is usually easy, but the affected mother may rarely have an inactive disease.

The maternal disease is usually pemphigoid gestationis (herpes gestationis), an autoimmune subepidermal bullous disease associated with pregnancy.¹⁴ Newborns from mothers with pemphigus vulgaris may suffer from neonatal blisters and mucosal lesions.¹⁵

A NEWBORN WITH VESICLES An Emergency: Rule Out Herpes

Neonatal herpes simplex virus (HSV) infection is rare but due to the misleading clinical features and the risk of severe

sequelae, this diagnosis is often discussed and acyclovir treatment started early on a presumptive basis.¹⁶

Intrauterine HSV disease is rare but is unlikely to be missed due to the extent of involvement of affected babies. Infants acquiring HSV in utero typically have cutaneous manifestations (vesicles or erosions, scars, dyschromic macules, aplasia cutis, macular-papular rash), ophthalmologic anomalies, and neurologic severe disease.

Neonatal herpes is usually acquired perinatally from an infected mother. In the majority of cases, maternal herpes is unknown. The most frequent cause is primary HSV2 infection, but HSV1 and recurrences may also infect the newborn. As the infection is acquired during delivery, the symptoms are delayed from birth (5 days to 1 month).

There are three forms of neonatal herpes:

- *Skin, eye, and mucous membrane (SEM) infection (50% of cases):* There is no internal dissemination and the prognosis is good.
- *Encephalitis (40% of cases):* Cutaneous lesions may not be present. The prognosis is severe, with possible sequelae in spite of acyclovir treatment.
- *Disseminated herpes (10%):* Newborns appear septicemic, with fever, neurological signs, and multisystemic involvement (lung, liver, eye). Cutaneous lesions are present in half of the cases. Even with treatment, mortality is high, and survivors often suffer from ocular and neurological sequelae.

The dermatologist may diagnose neonatal herpes by clinical examination showing isolated or grouped 1–3 mm vesicles, with a slight surrounding erythema (Figure 7.6) on the skin or more rarely the oral mucosa; however, vesicles are not always present and herpes may manifest as nonspecific erosions.

The diagnosis may be rapidly confirmed by the following tests:

- Viral cultures from the mouth, nose, pharynx, eye, skin swabs, blood buffy coat, and CSF
- PCR testing of skin or mucous membrane lesions, blood, CSF
- Direct immunofluorescent staining for HSV



Figure 7.6 Neonatal herpes simplex. (Courtesy of Alain Taïeb, MD.)



Figure 7.7 Neonatal varicella.

The treatment is intravenous acyclovir, 20 mg/kg every 8 hours during 14 or 21 days.

Varicella

Congenital varicella, acquired in utero from a maternal varicella between the 13th and the 20th weeks of pregnancy, is rare.¹⁷ It may result in limb abnormalities, and ocular and neurologic involvement. The cutaneous lesions are irregular scars, sometimes zosteriform, atrophic areas, and hemorrhagic blisters.

Perinatal varicella is a very severe disease, occurring when the mother suffers from varicella between 5 days before and 2 days after delivery. The newborn has a disseminated, vesicular eruption (Figure 7.7), as well as visceral varicella (lung, liver). Specific immunoglobulins may prevent or lessen the severity of neonatal varicella.¹⁸ Acyclovir and supportive therapy are needed. The varicella vaccine should eradicate this severe disease.

Incontinentia Pigmenti

Incontinentia pigmenti is an X-linked dominant genetic disorder, occurring almost only in girls.¹⁹ It is due to mutations of the *NEMO* gene, located in X q 28. Inflammatory vesicles in a Blaschkoid pattern are the first clinical manifestation of IP. Papular, keratotic, then pigmentary lesions may follow or coexist. Eosinophils are found in the vesicles, and there is at the same time a blood hypereosinophilia. Incontinentia pigmenti is usually a benign, limited disorder, but may include neurological (epilepsy, mental retardation), ocular, and dental abnormalities, requiring specialized investigations.

A NEWBORN WITH PUSTULES

An Emergency: Rule Out Congenital Candidosis

Vesicular-pustular lesions are frequent in the neonate.²⁰ The majority are transient and benign, but they may also reveal a staphylococcal folliculitis, or a fungal infection, mainly due to *Candida albicans*. Cytological and mycobacteriological direct examination of the content of a pustule is a fast and inexpensive efficient diagnostic procedure.

The incidence of *Candida* infections increases in neonatology units, in part due to the use of wide-spectrum antibiotics. Contamination is mainly maternal-fetal but also nosocomial, mainly in premature infants, where cutaneous candidosis becomes systemic, with a severe prognosis.

Newborns may have localized *Candida* infections: oral thrush, perianal diaper dermatitis, nail infection with paronychia.

Congenital Cutaneous Candidosis

Congenital cutaneous candidosis is acquired in utero from a candidal chorioamnionitis. It is manifest at birth or shortly after, as a generalized rash, made of dozens of small erythematous papules that rapidly progress to vesicles and pustules (Figure 7.8), followed by superficial desquamation. Respiratory infection can be found, but systemic dissemination is rare, in contrast with systemic candidosis, which may also include skin lesions. Intravenous antifungal therapy is required if there is evidence of pneumonia or a birth weight less than 1500 g. In healthy term newborns with localized cutaneous candidosis, a topical antifungal treatment is sufficient.

Invasive Fungal Dermatitis

Invasive fungal dermatitis is a severe systemic infection occurring only in extreme premature babies (birth weight <1000 g).²¹ The fungi (organisms other than *Candida albicans* may be responsible) invade the body through the skin, due to the absence of an efficient epidermal barrier. This disseminated dermatitis starts a few days after birth as an erythematous crusty eruption, with erosions and pustules (Figure 7.9). As in all forms of superficial candidosis, fungal filaments are easily found in the lesions. Prolonged parenteral antifungal therapy and supportive care are necessary. Prognosis is severe, and sequelae may occur, depending on the delay in treatment.^{22,23}

Benign Neonatal Pustuloses²⁴

Toxic erythema of the newborn occurs in one third of term newborns. It is a diffuse papular eruption that lasts for a few days. The center of the lesions may be vesicular or pustular and some cases are predominantly pustular. Tzanck smear shows eosinophils. The pathophysiology is unknown, and there is no



Figure 7.8 Congenital cutaneous candidosis.



Figure 7.9 Invasive fungal (*Candida albicans*) dermatitis.

clinical consequence. Transient neonatal pustular melanosis is a variant of erythema toxicum, leaving pigmented macules in dark skin. A transient neonatal pustulosis probably in relation with *Malassezia* colonization has been described²⁵ (Figure 7.10). Topical antifungals are rapidly effective. This benign pustulosis should not be confused with neonatal acne, where comedones are the main lesion.

Infantile acropustulosis is a rare pustulosis of infants, predominating on the hands and feet. It must not be mistaken for scabies but may follow an efficiently treated scabies.

Scabies

The incubation period of scabies is around 15 days, and a newborn may be contaminated by the cutaneous contact of an infested individual. The newborn does not express pruritus. The skin lesions are a papular-vesicular eruption, with small nodules predominating around the axillae, vesicles or pustules

on the palms and soles. Burrows may be seen by a naked eye, and dermatoscopy may identify the intraepidermal mite. The contaminating individual is usually rapidly found.

First-line treatment for neonatal scabies is a scabicide product containing pyrethrinoids. Care must be taken about the decontamination of the linen, the treatment of contact individuals, and the avoidance of repeated or toxic treatments.

A NEWBORN WITH A MACULAR/PAPULAR RASH Neonatal Sepsis

Neonatal sepsis is a worldwide problem and a leading cause of mortality in newborns. Prevention and treatment strategies have been discussed.²⁶ Cutaneous symptoms are not infrequent in neonatal sepsis, but the majority, including macular-papular rashes (Figure 7.11), are nonspecific.²⁷ Neonatal sepsis is a multisystemic disease. Many microorganisms may be involved, such as streptococci, salmonellas, hemophilus, *Escherichia coli*, and CoNS. The diagnosis must systematically be suspected and appropriate biological examinations performed. The availability of superficial lesions is important for the bacteriological identification of the causing organism. The prevention of neonatal sepsis relies on adherence to strict hospital hygiene protocols, avoidance of skin trauma, and limitation of invasive procedures in neonatal intensive care.²⁸

Listeriosis

Listeria monocytogenes is a rare cause of maternal-fetal infection. Affected mothers, contaminated by food, develop a flu-like febrile illness before onset of labor. Infants appear septicemic with a multisystemic involvement. Cutaneous lesions are present at birth. A macular-papular generalized rash, with petechiae, progresses to vesicles then pustules. Gram-positive rods can be found in the pustules. Immediate antibiotic treatment is needed, using ampicillin and an aminoglycoside.

Viral Infections

Enteroviruses, and more rarely other viruses, can infect newborns, with consequences ranging from asymptomatic infection and benign illness, to severe, life-threatening disease.²⁹



Figure 7.10 *Malassezia*-induced cephalic pustulosis.



Figure 7.11 Nonspecific macular rash in a *Salmonella* sepsis.



Figure 7.12 Neonatal lupus erythematosus.

Frequently occurring symptoms include fever, irritability, lethargy, anorexia, and nonspecific rash. Diagnosis may be done by viral isolation in tissue culture or polymerase chain reaction.

Lupus Erythematosus

Neonatal lupus erythematosus (NLE) is due to the transplacental transfer of antinuclear antibodies (anti-Ro-SSA, more rarely anti-LA-SSB). Mothers may be asymptomatic or suffering from a connective tissue disease. The autoantibodies are pathogenic for the skin and the cardiac-conducting tissue. Cutaneous NLE consists of annular papulosquamous lesions, located on the upper part of the face and scalp (Figure 7.12). They disappear in a few weeks. NLE may also cause congenital heart block and, rarely, liver disease and hematologic manifestations.³⁰

TORCH Syndrome

TORCH is an acronym designating a clinical condition that can be caused by several congenital infections: *Toxoplasmosis*, *Other infections*, *Rubella*, *Cytomegalovirus*, *Herpes*. Clinical manifestations are nonspecific: they include petechial purpura, jaundice, nodules, and rashes.

The “blueberry muffin baby” (purple papules) is a very rare condition secondary to the persistence of fetal cutaneous nodules of erythropoiesis³¹ (Figure 7.13).

In addition to these severe fetal infections, dermal hematopoiesis may be due to a severe hemolysis or a malignant condition (neuroblastoma, rhabdomyosarcoma, histiocytosis, or congenital leukemia).

A NEWBORN WITH SUBCUTANEOUS NODULES

Subcutaneous fat necrosis of the newborn is a benign panniculitis occurring in newborns with some risk factors.³² Subcutaneous nodules, starting shortly after birth, are located on the upper back, shoulders, and arms (Figure 7.14). Recently, subcutaneous fat necrosis has been reported as a complication of whole-body cooling performed in order to prevent brain sequelae in infants with birth asphyxia and hypoxic ischemic



Figure 7.13 Bluish nodular eruption (blueberry muffin baby) during a CMV infection. (Courtesy of Odile Enjolras, MD.)

encephalopathy.³³ Complications of fat necrosis include hypercalcemia that should be monitored and treated, pain, dyslipidemia, renal failure, and subcutaneous atrophy. Clinicians should be aware of the possible complication of fat necrosis and continue to monitor infants for skin changes in the weeks following therapeutic hypothermia.



Figure 7.14 Subcutaneous fat necrosis after cooling therapy.

A NEWBORN WITH AN ULCERATION: ECTHYMA GANGRENOSUM

Pseudomonas aeruginosa infection may result in a severe necrosis of the skin, known as ecthyma gangrenosum (Figure 7.15). Initially bullous and/or pustular, ecthyma gangrenosum is an impressive ulceration, usually in a baby with severe systemic sepsis. Rarely, other pathogens have been reported to induce such tissue losses.

A NEWBORN WITH ERYTHRODERMA An Emergency: To Prevent Dehydration and Superinfection

Erythroderma, i.e., generalized erythema and desquamation, can occur in newborns.³⁴ This must be differentiated from toxic erythema (SSSS), generalized mastocytosis (skin infiltration, bullae), ichthyosis bullosa (erythema, hyperkeratosis, bullae), and intense physiological desquamation of the newborn.

Erythroderma induces a cutaneous insufficiency. Affected newborns are at risk of superinfections, as well as metabolic complications due to the cutaneous losses of water, electrolytes, and proteins. They require *intensive neonatal care* and careful investigation and follow-up. Cutaneous management is based on emollients and prevention of infection. Systemic toxicity from topicals must be carefully prevented.

Causes of Neonatal Erythroderma

The main causes of neonatal erythroderma are inherited ichthyoses. Rarer causes include immunodeficiencies (Omenn syndrome), inflammatory dermatoses such as psoriasis, seborrheic dermatitis (Leiner disease) or atopic dermatitis, and some metabolic disorders.

Inherited ichthyoses are a group of genetic skin diseases characterized by excessive desquamation. Some of these disorders can be present at birth. The clinical presentation is a neonatal erythroderma, or a collodion baby.

The *collodion baby* is a striking phenotype: the baby seems to be surrounded by a shiny, erythematous envelope



Figure 7.16 Collodion baby. (Courtesy of Claudine Blanchet-Bardon, MD.)

resembling cellophane or collodion. Tension around the eyes and the mouth gives rise to eclabion and ectropion (Figure 7.16). The collodion-like envelope soon fissures and desquamates. Collodion babies are at risk of dehydration, hypothermia, and infection from an inefficient skin barrier, and they must be cared for in incubators. Collodion babies must be differentiated from the collodion-like hyperkeratotic aspect of some ectodermal dysplasias. Although the majority of collodion babies are due to variants of congenital ichthyoses,³⁵ some cases rapidly recover, with a perfectly normal skin. It is impossible to predict the outcome during the first days or weeks.

Netherton Syndrome

Netherton syndrome is characterized by a unique form of ichthyosis (ichthyosis linearis circumflexa), trichorrhexis invaginata, and atopic dermatitis. This syndrome is due to mutations of the gene *SPINK5*, which codes for a protease called LEKTI. Affected children may be erythrodermic at birth (Figure 7.17). In this condition, the epidermal barrier is severely impaired, and there is a risk of hypernatremic dehydration, as well as systemic intoxication from absorbed topical drugs. The same risk exists, at a lesser degree, in all erythrodermic infants and, as said, in collodion babies.

A NEWBORN WITH PURPURA

Apart from traumatic purpura resulting from difficult delivery, purpura in a newborn is always an emergency. The main causes are platelet abnormalities, coagulation defects, and infections.



Figure 7.15 Ecthyma gangrenosum.



Figure 7.17 Neonatal erythroderma of Netherton syndrome.

Neonatal purpura fulminans is a clinical-pathologic entity of dermal microvascular thrombosis with disseminated intravascular coagulation and perivascular hemorrhage. The clinical presentation is the rapid onset of large cutaneous purpuric lesions (Figure 7.18). It is usually fatal if not promptly recognized and treated. The two main causes of neonatal purpura fulminans are congenital protein C or protein S deficiency, and severe infections (group B streptococci, meningococci) causing a consumptive coagulopathy and a relative deficiency of protein C and/or S. Other causes are rare. Replacement therapy is urgent.³⁶



Figure 7.18 Neonatal purpura fulminans.

Thrombocytopenic purpura is frequent and calls for an urgent prevention of brain hemorrhage. Neonatal thrombocytopenia is due to maternal antiplatelet antibodies. The two causes are maternal autoimmune diseases (autoimmune thrombocytopenia or lupus erythematosus) and maternal alloimmunization against fetal platelet antigens inherited from the father. In this case, the maternal platelet count is normal. The most important platelet antigen system involved is HPA-1. Intravenous immunoglobulin therapy is indicated and if platelet transfusion is required, it is mandatory to investigate compatibility with the donor. This diagnosis is important for the follow-up of future pregnancies.

A NEWBORN WITH A SKIN TUMOR Hemangiomas and Other Vascular Tumors

Infantile hemangiomas usually become visible after a few weeks. At birth, they may be mistaken for capillary angiomas. White vasoconstriction areas may herald the development of a hemangioma.

Infantile hemangiomas proliferate during the first weeks of life, and their growth may induce complications such as a functional impairment due to a periorificial location, disfigurement, excessive growth, ulcerations, superinfection, pain, etc. Treatment with oral propranolol induces a rapid regression of these threatening hemangiomas.³⁷

Congenital hemangiomas³⁸ are usually diagnosed prenatally. They realize violaceous superficial tumors (Figure 7.19). Some of them regress rapidly. If the diagnosis of hemangioma cannot be ascertained clinically, a biopsy is necessary.



Figure 7.19 Congenital hemangioma.

Tufted angioma and kaposiform hemangioendothelioma are rare vascular tumors, which may be present at birth. They are associated with the Kasabach-Merritt phenomenon (life-threatening thrombocytopenia and coagulopathy).

Hamartomas

Localized cutaneous malformations are visible at birth. Epidermal nevi, melanocytic nevi, and other hamartomas must be diagnosed rapidly. The areas of concern are the needed work-up, the specialized medical-surgical management, and the psychologic support to the parents.

Infantile myofibromatosis appears at birth as cutaneous nodules that may be solitary or multiple. Skin lesions may regress spontaneously, but visceral lesions may be fatal.

Mastocytosis

Mastocytosis is a benign infiltration of the skin by mast cells. Several forms exist,³⁹ which may be present at birth. Darier sign is a useful clinical clue: the gentle rubbing of the lesion induces an urticarial papulation. This must be done on a very small area, to avoid generalized flushing.

Mastocytoma is a round elevated nodule, usually solitary.

Diffuse cutaneous mastocytosis presents as large orange or brown thick plaques (Figure 7.20). Urtication or bulla formation may be the consequence of pressure or friction by clothes.

Urticaria pigmentosa is the name given to papular mastocytosis, which develops later in infancy.



Figure 7.20 Diffuse cutaneous mastocytosis.



Figure 7.21 Subcutaneous metastasis of neuroblastoma. (Courtesy of Aïcha Salhi, MD.)

Neoplastic Diseases

Langerhans cell histiocytosis (LCH) is a polymorphous disorder. It cannot be considered as an emergency, but it is important to suspect LCH, when a newborn has papular-crusty, sometimes purpuric lesions in the folds, the scalp, and the diaper area (Letterer-Siwe disease). Visceral, bone involvement, as well as diabetes insipidus, may be present. Hashimoto-Pritzker disease is a nodular, spontaneously regressive form of LCH.

Neuroblastoma may be present at birth. Cutaneous metastases appear as firm, bluish nodules (Figure 7.21), which may blanch on palpation. Histologic examination will differentiate these lesions from leukemia, or nonneoplastic causes of “blueberry muffin” lesions.

Leukemia is rarely congenital. Purpuric and nodular lesions appear in the context of a systemic leukemia. Biopsy and blood examinations provide the precise diagnosis.

Rhabdomyosarcoma is a malignant tumor that can be congenital. It appears as a shiny, red to purple firm tumor. Usual locations are the head and neck and the perineal area.

Congenital melanoma is a rare occurrence. It may present as a nodule on a giant congenital melanocytic nevus.

In all of these cases of neonatal cutaneous tumors, the diagnosis relies on the histologic examination of a biopsy, which may be considered as urgent. Special stains may be necessary.

A NEWBORN WITH A LOCALIZED ABSENCE OF SKIN

Aplasia cutis is a congenital absence of skin, on a limited area. The majority of cases are small round atrophic patches of the scalp, near the vertex, with no associated anomaly.

Other situations include associations with epidermolysis bullosa (Bart syndrome), malformative syndromes, and chromosomal defects.⁴⁰

Some cases of aplasia cutis are large congenital ulcerations requiring careful wound care. Large ulcerations of the scalp may involve the underlying structures, with the risk of lethal hemorrhages of the venous system. Radiologic imaging and surgery may be necessary.

CONCLUSIONS

Neonatologists are experts in the clinical care of high-risk newborns, including the urgent diagnosis of infections and the multisystemic dimension of all acute conditions. Dermatologists are experts in the clinical analysis of skin lesions, leading to the diagnosis of urgent and nonurgent, transient or lasting conditions. Their cooperation is needed for the best evaluation and treatment of newborns with dermatological conditions.

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Necrotizing soft-tissue infections

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BACKGROUND AND CLASSIFICATION

Skin and skin structures are among the most frequent sites of human bacterial infection and account for ~10% of hospital admissions in the United States.¹

The terminology used for infections of skin and skin structures is often confusing. “Primary” skin infections occur in otherwise normal skin and are usually caused by group A streptococci or *Staphylococcus aureus*. Infections are called “secondary” when they complicate chronic skin conditions (e.g., eczema or atopic dermatitis).

A second classification system divides skin and skin structure infection into “uncomplicated” or “complicated,” the latter defined as involving abnormal skin or wound infections occurring in a compromised host or requiring substantial surgical intervention.

A more important and, for our purposes, a more relevant distinction, with essential management implications, subdivides soft-tissue infections into “necrotizing” and “necrotizing” processes. This chapter will review only the necrotizing soft-tissue infections (NSTIs), the ones that pose real emergencies that are rapidly progressive, destructive, and highly lethal.

NSTIs can be defined as infections of any of the layers within the soft-tissue compartment (dermis, subcutaneous tissue, superficial fascia, deep fascia, or muscle) that are associated with necrotizing changes. NSTIs are typically not associated with abscesses, although they can originate from an untreated or inadequately drained abscess.

The incidence of NSTIs in the United States, as recently established from insurance databases from various states, is 0.04 cases per 1000 person-years.² This is often enough to predict that surgeons, family physicians, internists, and dermatologists will encounter at least one patient during their practice but too infrequently for acquiring any real degree of familiarity with the disease. Distinguishing necrotizing from nonnecrotizing soft-tissue infection and establishing the diagnosis of these infections is probably the greatest challenge in managing them. Early diagnosis and aggressive surgical debridement of these often fatal and crippling diseases will save patients’ lives and reduce morbidity. It is for this reason that familiarity with the clinical characteristics, diagnostic tools, and principles of management is so important when dealing with affected individuals.

Necrotizing fasciitis (NF) is categorized as type 1, 2, or 3, depending on the causative organisms.³ Type 1 NF is mostly a mixed infection from aerobic and anaerobic bacteria, including group A β -hemolytic streptococci, *Staphylococcus aureus*, *Klebsiella* species, and Enterococci, *Escherichia coli*, *Clostridium*, and *Bacteroides* species. The infecting organisms are often introduced at sites of surgery or trauma, and the lesions are often found in perineal and abdominal areas.

Type 2 NF is caused by group A β -hemolytic streptococci (GAS), possibly with a coinfection by *S. aureus*, and primarily affects the extremities.

Type 3 NF is associated with *Vibrio vulnificus*, which enters the subcutaneous tissues via puncture wounds from fish or marine insects.

Another similar classification¹ distinguishes among the following subgroups of NF:

1. Polymicrobial fasciitis (type I)
2. Fournier gangrene
3. Synergistic necrotizing “cellulitis” with fasciitis and myonecrosis
4. Streptococcal gangrene (type II)
5. Fasciitis due to *V. vulnificus* and other *vibrio* species

Myonecrosis is further subdivided into crepitant myonecrosis and noncrepitant myonecrosis.

Anatomical boundaries are not necessarily respected by invasive pathogens, and one form of infection can rapidly progress to another, e.g., cellulitis can progress to fasciitis and myonecrosis and vice versa.

CLINICAL PRESENTATION AND LABORATORY AIDS REQUIRED FOR DIAGNOSIS

We briefly describe an actual case that emphasizes the essence of early diagnosis:

One of us (RW) was called for a consultation in the rheumatology clinic to examine a 26-year-old woman with SLE due to severe pain in the hip area. The affected skin was erythematous and—we’ll get ahead of ourselves here—it had a giveaway color, something between pink and violet, a color that once you see, you will never miss. She was febrile but appeared to be in good physical condition. She had sought consultation independently. We prescribed a combination of ampicillin with clavulanic acid and instructed her to return the following week. Instead, she presented on the same evening to the emergency room with worsening of the pain that was now unbearable. Because nothing in her clinical situation seemed to have changed, the consultant dermatologist ordered an x-ray, which showed no bone or joint involvement, and so he discharged her with the same medication. She returned to the emergency room on the following morning and died 1 day later from septic shock (the result of cultures were GAS) and multiorgan failure. What we want to emphasize in this tragic case is the paucity of dermatologic signs and the absence of systemic manifestations except for severe localized pain. There were no signs of either sepsis or shock when we first saw the patient.

An excellent representative case was described in a systematic review of periorbital NF⁴:

Presentation: The patient, a 49-year-old man, presented three consecutive times to his local hospital with redness and localized painful swelling of the left upper eyelid that was diagnosed as a sty. There had been no improvement after self-care treatment and topical antibiotics. Throughout the next few days, the left eyelid erythema and swelling markedly worsened. He experienced generalized malaise, chills, rigor, and vomiting, and he was admitted to the emergency room, where he was febrile, tachycardic, and hypotensive. A neurologic examination showed signs of spontaneous decerebration. He also had chronic lymphocytic leukemia, for which he had received a cycle of induction chemotherapy with fludarabine, cyclophosphamide, and rituximab.

A group from Glasgow has published a case of NF in a 6-year-old girl “without associated skin changes.”⁵ The alleged absence of skin changes (citation from the title) turned out to be “without typical skin changes,” and the patient’s “right limb was erythematous with tenderness in the right knee,” actually the classic presenting signs of NF.

It is our experience that too many cases of NF are misdiagnosed as nonnecrotizing skin infections, and vice versa. This is also the experience of others. In a large case-series⁶ of NF, only 14.6% of the patients were correctly diagnosed or suspected as having NF on admission. The majority of the patients were diagnosed as having cellulitis (58.4%) or abscesses (18%). Similar figures were recorded on the case report forms of 42 cases of GAS NF at the Florida Department of Health.⁷ Only 9.5% were correctly diagnosed as having NF, and 4.8% were diagnosed as suffering from invasive GAS disease or toxic shock syndrome (also an acceptable diagnosis), but 31% of the patients had an admitting diagnosis of cellulitis and 24% of sepsis. The mean percentage of misdiagnosis is an alarming 71.4%, as revealed in a published systematic literature search⁸ comprising case series of 50 or more subjects with NF.

The reason for this is, in our opinion, the enormous dread of discovering that our patient is suffering from “flesh-eating disease” together with the erroneous expectation that the clinical signs should be suitably dramatic.

Clinicians should be aware that the pathologic process involved in NF takes place very deeply, i.e., at the level of the fascial planes and even deeper, thus sparing the top layers of the skin at the earliest stages. This is unlike cellulitis that involves the dermis and subcutaneous tissues early on, and much different from erysipelas, the most superficial infection. Consequently, clinical signs, e.g., the color, hemorrhagic bullae, and necrotic skin ulcers, are more prominent in the more superficial skin infections and less noticeable in the deeper ones. Erysipelas would appear to the inexperienced clinician as being more serious than cellulitis, and cellulitis more alarming than NF. It cannot be emphasized enough that the very early stage of NF, the time when we strive to make the correct diagnosis, is characterized by mild signs that provide no clues of the seriousness and grave prognosis of the disease. Most of the patients we saw were febrile, but in apparent good health, and came for consultation independently with no need for special transportation. This is also the experience of others.⁹ The affected dermal area characteristically had the typical rose-violet color. One sign that no report misses is the disproportionately severe pain at the site of involvement. Another clue to diagnosis is the tenderness extending beyond the apparent area of involvement.



Figure 8.1 This baby was hospitalized in the pediatric department and diagnosed as suffering from cellulitis. An improvement in the general and local condition of the patient was noted and documented in the chart on the following morning. That evening, however, the entire anal area underwent necrosis, as seen here. She underwent immediate surgery at another hospital, and survived. Note the mild erythema surrounding the necrotic area.

The explanation for this phenomenon is the rapid spread of the infection along the deep fascia, faster than in the epidermis.

Another cause and possible explanation for misdiagnosis or delay in diagnosing NF is the search for specific findings, which are either not as common as previously thought, or, more importantly, are signs that became apparent only later in the evolution of the disease (Figure 8.1). These include the presence of crepitus on physical examination or soft-tissue air on plain x-ray, hemorrhagic and gangrenous bullae plus ulcers, and the appearance of the compartment syndrome (one of the favorite signs of the orthopedic surgeons). Pathognomonic as all these signs may be, waiting for them to emerge would lead to a regrettable and unfortunate postponement in arriving at the correct diagnosis. According to some large, retrospective case series^{6,9–11} and reviews,¹² the most common symptom of NF is pain (>97%), and the most common clinical findings on admission are erythema, tenderness, and warm skin on palpation (>90%–100%). Much less common and inconsistent symptoms and signs are fever and tachycardia (40%–70%), bullae/vesicles formation (20%–40%) and discoloration (20%–40%). Still less common are crepitations (12%–25%), x-ray findings (~20%), skin necrosis, and hypotension, which are also late signs.

A more recent systematic literature search further supports these findings.⁸ It included case series of 50 or more subjects with information on symptoms and signs at initial presentation, and nine case series were selected, with a total of 1463 patients. Swelling was the most frequent sign (80%), followed by pain and tenderness (79%) and erythema (70%). Only 40% of patients had fever, 24% had skin necrosis, and as few as 20.3% had crepitus. Although the most common presentations of pain/tenderness, swelling, and erythema were the same as in previous studies, they appeared less frequently.

Patients with NF may progress with alarming rapidity from the early and intermediate to the late presentations within hours of initial insult, and these patients may present with “hard signs” on admission; however, this is not the rule, and these cannot and should not be considered early signs.

Keys to Early Diagnosis

- Do not expect to see a severely ill patient with signs of septic shock. NF patients are very often in apparently good health, and present just like ordinary otherwise fit patients.
- Do not expect to see an alarming local manifestation that correlates with the gravity of the disease.
- Do not look for the “hard signs,” such as necrosis, crepitation, x-ray findings, or compartment syndrome. These are late signs and, in any event, are present in the minority of patients.
- Do look for severe disproportionate pain extending beyond the area of skin involvement.
- Do look for swelling and tenderness that usually extends beyond the area of skin involvement.
- Do look for the very typical color of the erythema that is not as intensive as in the more superficial infections (erysipelas and cellulitis) and does not have distinct margins.
- Do look for a rapid progression of the disease despite the use of antibiotics.
- Do look for the new triad of symptoms: local pain/tenderness, swelling, and erythema.^{8,13}

Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC)

A novel diagnostic scoring system has been designed for distinguishing NF from other soft-tissue infections based on laboratory tests routinely performed for evaluating the latter: the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC).¹⁴ This compares a set of laboratory findings between patients with and without NSTIs and identified six independent variables associated with NSTIs. The presence of each variable gives a specific number of points toward the final score. Table 8.1 shows the scoring system.

The total score has a range of 0–13, and patients can be categorized into three groups according to the risk of NF. Patients with an LRINEC score ≤ 5 have a <50% probability of NF, patients with a score of 6–7 have a moderate risk with a

50%–75% probability, and those with a score >8 have a probability of 75% and above.

The model has a positive predictive value of 92% and a negative predictive value of 96% at a cutoff score of ≥ 6 . A score of ≥ 8 is strongly predictive of NF, with a positive predictive value of 93.4%.

We agree that this score constitutes a valuable tool for both confirming and ruling out an NF. It has the additional advantage of being based on laboratory variables that are widely available across different institutions; however, “it should be emphasized that the diagnosis of NSTI is a clinical diagnosis, and this diagnosis or even suspicion of it warrants immediate operative debridement.” ... “This is an adjunct in the management of soft tissue infections. Clinical acumen remains of paramount importance, and when the clinical suspicion is high, emergent debridement must be performed regardless of the LRINEC score.” All the changes in the laboratory variables are indicators of sepsis and they had been known for years.

An accompanying editorial¹⁵ expressed doubts and concerns about the practical value of this tool in early diagnosis. “Suspicion of NSTI, in the opinion of many authorities including myself, should prompt exploration of the affected area in the operating room without delay. To the extent that identification of a high-risk patient by the LRINEC score leads to additional diagnostic testing (e.g., computed tomography...), the process becomes ‘paralysis by analysis’ and life and limb are placed in peril by the delay engendered.” We believe that these very tough caveats are entirely well taken and that they should be stringently implemented but they are not specific solely to LRINEC.

Some subsequent analyses, however, have noted that the LRINEC score is not quite as accurate as first reported. In one subsequent review, the LRINEC scoring system demonstrated a positive predictive value of 25%–57% and a negative predictive value of 80%–95%, bringing its utility and practical value into question.¹⁶

A retrospective evaluation¹⁷ of laboratory-based diagnostic tools for cervical NF reported that a LRINEC score of ≥ 6 had a sensitivity of 56% and a specificity of 60%, and a positive predictive value of 25%, and a negative predictive value of 85%. A surgically confirmed case of NF was presented in an interesting case report from the emergency department (ED) in the San Diego Health System,¹⁸ in which the LRINEC score was initially 0 although the patient had presented to the ED 3 days after the onset of symptoms.

Comorbidities and Risk Factors

The incidence of NF has been varied in worldwide reporting, i.e., its global prevalence reported as being between 0.4 and 1.3 cases per 100,000 population in Canada and the United States.¹⁹

Trauma is the most common identifiable etiology. The majority of patients have a history of minor or major traumas, generally involving external injuries and surgical wounds; likewise, a recent varicella infection is also a risk factor for NF in children²⁰; however, the policy of immunization will probably eliminate it with time.

There are several risk factors that predispose to the disease; however, the authors think that too much emphasis has been placed upon them, and we suggest not looking for and/or relying on risk factors when diagnosing a specific patient. Several groups have reported²¹ that more than half the patients developing NF have one preexisting medical condition, and 35% of them have at least two. The most frequent comorbidity in patients with NF is diabetes mellitus. The prevalence

Table 8.1 Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) Score

Variable, units	Score
C-reactive protein, mg/L	
<150	0
≥ 150	4
Total white cell count, per mm ³	
<15	0
15–25	1
>25	2
Hemoglobin, g/dL	
>13.5	0
11–13.5	1
<11	2
Sodium, mmol/L	
≥ 135	0
<135	2
Creatinine, $\mu\text{mol/L}$	
≤ 141 (≤ 1.6 mg/dL)	0
>141 (>1.6 mg/dL)	2
Glucose, mmol/L	
≤ 10 (≤ 180 mg/dL)	0
>10 (>180 mg/dL)	1

of diabetes mellitus in patients with any type of NF ranges between 30% and 60%.¹³ Other common comorbidities include immunosuppression, liver cirrhosis, chronic heart failure, pulmonary disease, malignancy, obesity, alcohol abuse, systemic lupus erythematosus, Addison disease, chronic renal failure, and peripheral vascular disease.^{13,21}

Treatment

The therapy for NF involves the principles of treatment of any kind of surgical infection: source control, antimicrobial therapy, support (hemodynamic, nutritional), and monitoring. NF is an excellent example of the important role of source control. When treatment is based only on antimicrobial therapy and support, mortality approaches 100%.^{22,23} Antibiotics have not been shown to halt the infection in NF, when pre- and postantibiotic series are compared.²³ Early and complete debridement is essential for effective treatment of NF. Concomitantly, appropriate broad-spectrum antibiotic coverage, combined with adequate organ support and close monitoring, helps patients during the acute phase of the disease, but, again, it is only the complete debridement of infected tissue that controls the infection and allows for future recovery.

Wide debridement of all necrotic and poorly perfused tissue at the time of initial presentation is clearly the most important step. The debridement is extended until skin and subcutaneous tissue cannot be elevated off the deep fascia by a gentle forward pushing maneuver. Healthy, viable, bleeding tissue should be present at the edges of the excision site, and aggressive resuscitation should accompany the perioperative period. Poorly perfused tissue is a nidus for continued bacterial proliferation. The anesthesiologist plays a critical role in the initial management for hemodynamic instability. Because NF fuels the progression of the septic state, one may not be able to stabilize completely the patient hemodynamically before surgery, and delay may lead to a fatal outcome. Once the initial debridement has been done, management in an intensive care unit is recommended, and scheduled debridements should be performed as necessary.

Physiologic support combined with close monitoring in an intensive care unit setting is mandatory. Appropriate nutritional (enteral or parenteral) support administered as early as possible cannot be overemphasized. The magnitude of protein and fluid loss from the large wounds associated with NF is tremendous. In general, patients with severe tissue loss should receive twice their basal caloric requirements.^{10,22} Aggressive fluid resuscitation and blood component therapy are often required during the perioperative period.

It is not uncommon to see patients with NF develop organ failure, such as acute renal failure (~30%), adult respiratory distress syndrome (~30%), multiorgan system dysfunction (20%), or infectious complications,²⁴ all of which require careful monitoring and prompt treatment.

As for the role of antibiotics in NF, we refer to the Infectious Disease Society of America guidelines.²⁵ Antimicrobial therapy must be directed at the pathogens and used in appropriate doses until repeated operative procedures are no longer needed, until the patient has demonstrated obvious clinical improvement, and until fever has been absent for 48–72 h.

Antimicrobials

The following antimicrobials are recommended for NF in the 2014 updated guidelines of the Infectious Diseases Society of

America for the diagnosis and management of skin and soft-tissue infections²⁵:

- Mixed infection (empiric treatment of polymicrobial NF)
 - Either vancomycin, linezolid, or daptomycin combined with one of the following options:
 - Piperacillin-tazobactam
 - A carbapenem (imipenem-cilastatin, meropenem, and ertapenem)
 - Ceftriaxone + metronidazole
 - A fluoroquinolone + metronidazole
- GAS infection (type II NF)
 - Penicillin + clindamycin
- *S. aureus* infection
 - Nafcillin, oxacillin, cefazolin, vancomycin (for resistant strains), or clindamycin
- *Clostridium* infection
 - Clindamycin + penicillin
- *Aeromonas hydrophila*
 - Doxycycline + ciprofloxacin or ceftriaxone
- *Vibrio vulnificus*
 - Doxycycline + ceftriaxone or cefotaxime

The recommendations of the World Society of Emergency Surgery (WSES) are similar²⁶:

- Empiric treatment of polymicrobial NF
 - Linezolid + piperacillin/tazobactam or
 - Daptomycin + piperacillin/tazobactam + clindamycin
- Fournier gangrene without signs of sepsis
 - Piperacillin/tazobactam + clindamycin
- Fournier gangrene with signs and symptoms of severe sepsis
 - Meropenem + linezolid

Until recently, therapy directed against methicillin-resistant *Staphylococcus aureus* (MRSA) was not recommended in standard guides, presumably due to the rarity of this pathogen as a cause of NF. Over the past few years, community-associated infections caused by MRSA (CA-MRSA) have become common in multiple areas in both the United States and worldwide, the majority involving skin and soft tissues. CA-MRSA should no longer be regarded as a strictly nosocomial pathogen.²⁷ During the past 10 years, MRSA has been the most common pathogen isolated from skin and soft tissues infections in the ED.²⁸ Fourteen cases of NF associated with CA-MRSA were identified among 843 patients whose wound cultures grew MRSA,²⁹ and wound cultures were monomicrobial for MRSA in 12 of them. Although all these patients survived, serious complications were common, including prolonged stays in the intensive care unit, the need for mechanical ventilation and reconstructive surgery, septic shock, nosocomial infections, and endophthalmitis. The main lesson from this and other reports is that we should include antimicrobials with good activity against CA-MRSA in the currently recommended therapy for NF.^{29,30} Vancomycin is still the preferred antibiotic for empirical coverage and definitive therapy, but whether it should remain so is questionable. It is a less effective antistaphylococcal agent than the penicillins, and increased use will further exacerbate problems with vancomycin-resistant enterococci and staphylococci.³⁰ Newer effective antimicrobials, such as linezolid and teicoplanin, represent appropriate empirical therapeutic options.²⁷

Single-organism NF is also increasingly recognized as a manifestation of *Klebsiella* infections.^{31–33} This is probably due

to the emergence of the highly virulent K1 capsular serotype, the predominant serotype of potentially lethal disseminated infection with this pathogen in Asia, including NF.³¹ Single-organism NF due to *Klebsiella* spp. is strongly associated with predisposing conditions, such as diabetes mellitus, and has a propensity for metastatic dissemination resulting in multiple sites of infection.³³

Hyperbaric oxygen, as an adjunctive treatment, has been advocated by different groups who argue for a decrease in the number of debridements and an associated decrease in mortality.^{10,34,35} Results from this therapeutic strategy are contradictory, and no real epidemiologically based studies have been performed to elucidate the effect of this form of therapy. Hyperbaric oxygen therapy should not jeopardize standard therapy for NF. Hyperbaric oxygen is not available at all institutions and is hardly standard equipment of ordinary intensive care units, thus patients would have to be transported to the chamber at least three times per day, which may expose them to risk of contamination and may limit the ability to perform close monitoring and timely debridements while they are in the chamber.

Another adjuvant treatment that has been used is intravenous immune globulin (IVIG). The value of this form of therapy is difficult to assess, given the small number of patients that had ever been treated with this method, the differences in methodologies, and particularly, the variations between the various batches of the different companies.³⁶ The use of IVIG has been advocated mainly for GAS infections. Information on the efficacy of IVIG in GAS bacteremia can be found in a publication of the Canadian Streptococcal Study Group.³⁷ They compared survival in 21 consecutive patients with streptococcal shock syndrome who had been given IVIG to that of 32 control patients who did not receive the therapy. Sixty-seven percent of the treated patients survived compared with only 34% in the control patients. A double-blind, placebo-controlled trial from northern Europe showed no significant improvement in survival for the IVIG group.³⁸ We suggest adopting the conclusion of the Infectious Disease Society of America²⁵ "that additional studies of the efficacy of IVIG are necessary before a recommendation can be made." We vigorously disagree with those who suggest that this therapy "may allow an initial non-operative or minimally invasive approach."³⁹ No therapy should tempt the surgeon to postpone surgery or to perform less mutilating and consequently less effective surgery.

Prognosis and Factors That Affect the Outcome

Many attempts have been made to understand the factors affecting mortality from NF. The fortunate rarity of the disease and the multiple factors that influence the outcome (such as causative agent, site of infection, and host factors) have paradoxically hampered the establishment of an effective scoring system. Objective estimation of the probability of death from NF would have provided an explicit basis for clinical decisions, aid in the understanding of the relative contribution of these specific prognostic criteria, and reduce the reliance on clinical intuition.

The mortality rates for NF vary considerably, ranging between less than 10% and reaching as high as 75%. The larger, more robust, retrospective case series have narrowed these rates to between 25% and 40%.⁴⁰ What is clear, however, is that the prognosis has improved considerably over the past two decades as a result of early recognition and improved supportive multidisciplinary measures.

In a retrospective analysis of 99 patients with NF treated in three tertiary care hospitals in Ontario, Canada,⁴¹ the overall mortality was 20%. Sixteen patients underwent amputation or suffered organ loss. There was a strong positive association between a patient's age and mortality, with the risk of death increasing by 4% every year. Apart from age, streptococcal toxic shock syndrome and immunocompromised status were independent predictors of mortality. There was also a significant association between diabetes and negative outcome. The anatomic sites of infection did not reach a level of significance in predicting outcome, with the exception of perineal infection, which was significantly associated with a negative outcome. Interestingly, the hyperbaric oxygen therapy group had a higher mortality rate compared with the nonhyperbaric oxygen therapy group.⁴¹

NECROTIZING SOFT TISSUE INFECTION CAUSED BY *VIBRIO VULNIFICUS*

Although *Vibrio vulnificus* (*V. vulnificus*) infections had probably occurred in ancient times (the first fatal infection was possibly reported by Hippocrates in the fifth century BCE⁴²), it was not until the reporting of the first case in 1987 (in Taiwan)⁴³ that an increased prevalence became apparent. Recent findings question an association with periodic prolongation of warmer weather and warmer water temperature in some parts of the globe.⁴⁴ *V. vulnificus* is considered one of the most dangerous waterborne bacterial pathogens, with a case fatality rate that may reach 50% for *V. vulnificus* septicemia. *V. vulnificus* is estimated to account for 95% of all seafood-related deaths in the United States.⁴⁵

Microbiology and Epidemiology

Vibrio vulnificus is a naturally occurring, gram-negative, halophilic bacterium of the noncholera group that is a free-living inhabitant of estuaries and marine environments throughout the world. *Vibrio* species have been found in warm coastal waters ranging in temperature from 9 to 21°C in geographically diverse regions that include the Gulf of Mexico, South America, Asia (Thailand, Taiwan, Hong Kong), and Australia.⁴⁶ The bacterium is frequently found in oysters, crustaceans, and shellfish (according to various reports, up to 50% of oysters and up to 11% of crabs are cultured positive during the peak summer⁴⁷).

Clinical Manifestations

The disease manifestations caused by *V. vulnificus* depend on the route of infection, with three recognized syndromes: (1) primary septicemia, which is classically linked to the consumption of raw oysters; (2) wound infection resulting from cellulitis caused by direct inoculation of the microorganism, which may result in tissue necrosis and secondary bacteremia (usually involving the exposure of chafed skin to salty water containing the microorganism or injuries associated with the cultivation and/or preparation of seafood); and (3) gastrointestinal illness, characterized by vomiting, diarrhea, or abdominal pain. Pneumonia and endometritis have also been reported. Skin lesions appear within 24–48 h of exposure. The disease process begins with localized tenderness followed by erythema, edema, and indurated plaques. A purplish discoloration develops in the center of the lesions and then undergoes necrosis, eventually forming hemorrhagic bullae or ulcers. These clinical manifestations occur in nearly 90% of patients and are most common on the lower extremities. Such findings are very different from those described earlier for NF. The reason for this

is that the infection usually starts superficially and is accompanied with cellulitis. In a survey from Israel,⁴⁸ for example, 57 out of 62 cases of necrotizing soft tissue infection caused by *V. vulnificus* developed cellulitis, and only four had NF.

The disease occurs mostly in immunocompromised host-associated diseases. In a study of 67 patients,⁴⁹ 27 (40%) had hepatic disease, 17 (25.4%) had chronic renal insufficiency, and 12 (17.9%) exhibited adrenal insufficiency.

The diagnosis of necrotizing soft tissue infection caused by *V. vulnificus* is difficult, because the signs of sepsis due to *V. vulnificus* do not differ from any other form of sepsis. This infection should be suspected in patients with a rapidly progressive inflammation of the skin and soft tissues following recent exposure to contaminated seawater or raw seafood, and possibly one of the associated predisposing diseases. Identifying the bacteria from cultures permits a definitive diagnosis. Gram-negative bacteria can be seen on Gram staining.

Treatment

Soft tissue infection by *V. vulnificus* represents a true surgical emergency. Early recognition and prompt aggressive debridement of all necrotic tissue are critical for survival and improve the rate of survival. The cause of death in most cases is multiple-organ failure, acute respiratory distress syndrome, or overwhelming sepsis. With appropriate early surgical intervention, mortality varies from 8.7% to 50%, depending on a number of variables.⁴⁹ Without surgical intervention, the disease is usually fatal, because antibiotics alone are ineffective against the large soft-tissue bacterial inocula resulting from the invasive nature of these infections. Widespread obliterative vasculitis, plus vascular necrosis and thrombosis of the supplying vessels, hinders the penetration of antibiotics to the affected area. As with other types of NSTIs and NF, debridement must be aggressive, all necrotic tissue with overlying skin should be excised deeply and beyond the necrotic area, and all necrotic fascias and fat should be removed until healthy viable tissue is evident. A second examination should be done within 24 h to assess the progression of the condition and check the need for further debridement.⁴⁹

In addition to aggressive surgical debridement, efficient and early presurgical antimicrobial treatment is also essential for management of *V. vulnificus* infection. Antibiotic use should be initiated as soon as the diagnosis is considered likely. The combination of cefotaxime and minocycline has demonstrated a better outcome than monotherapy with either drug alone.⁴⁹ This combination is also better than first- or second-generation cephalosporin. More recently, the fluoroquinolones have been demonstrated to be as effective as the combination of cefotaxime plus minocycline in vitro and in vivo.⁵⁰ The combination of quinolone plus cefotaxime has shown superior in vitro efficacy than either drug alone or the combination of minocycline plus cefotaxime.⁵⁰

All other measures to be taken are the same as other types of NF.

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Life-threatening bacterial skin infections

Richard B. Cindrich and Donald Rudikoff

Dermatologists are often called on to consult on severe life-threatening skin infections in the emergency department, hospital wards, and in their clinical practices. The observational skills of the dermatologic specialist enable him or her to differentiate conditions that are potentially fatal from those that may look horrific but are not life threatening. This chapter provides essential information on serious infections, many of which are not usually discussed in depth in most dermatologic texts. These include periorbital (preseptal) and orbital cellulitis, malignant otitis, meningococemia, Rocky Mountain spotted fever (RMSF), Mediterranean spotted fever, anthrax, tularemia, and infections with *Vibrio vulnificus*, *Aeromonas hydrophila*, and *Chromobacterium violaceum*. It is hoped that prompt recognition of these infections by the clinician will reduce morbidity and possibly be lifesaving.

PERIORBITAL (PRESEPTAL) CELLULITIS AND ORBITAL CELLULITIS

Background

Eyelid infections presenting with erythema and edema occur in children and adults and in some cases cause serious sequelae. Involvement of the orbit with bacterial infection can result in ocular damage, cavernous sinus thrombosis, and death. Preseptal cellulitis is an infection of the eyelids and surrounding skin anterior to the orbital septum (Figure 9.1).¹ This layer of fibrous tissue arises from the periosteum of the orbit and extends into the eyelids.² Infection posterior to the septum is referred to as orbital cellulitis. Although less common than preseptal cellulitis, orbital cellulitis is a much more serious condition with the potential for major sequelae. It is essential when confronted with a patient with eyelid infection to distinguish orbital cellulitis from preseptal infection and other entities that may present similarly. Whereas preseptal cellulitis often can be managed in an outpatient setting, orbital cellulitis requires hospitalization, intravenous (IV) antibiotics, and sometimes surgical intervention. Immediate ophthalmologic consultation should be obtained, and because the process may derive from sinus infection, otolaryngologic consultation is important.

Clinical and Laboratory Aids Required for Diagnosis

Distinction between preseptal and orbital cellulitis in patients with periorbital inflammation is the major priority. Patients with preseptal cellulitis complain of pain, symptoms of conjunctivitis, epiphora (excessive tearing), and blurred vision and have eyelid and periorbital erythema and edema that may be so severe that they cannot open the eye.³ Although edema may frustrate examination, the visual acuity, light reflexes, and range of motion of the globe should be assessed. Unlike

preseptal cellulitis, orbital cellulitis presents with some degree of ophthalmoplegia (weakness or paralysis of eye muscles), pain on eye movement, and/or proptosis. The latter condition may also compromise the optic nerve causing vision loss, abnormal papillary reflexes, and disk edema. Computed tomography with contrast should be undertaken when physical examination is impeded by obtundation or patient age to rule out abscess formation, if orbital cellulitis is suspected.

Orbital cellulitis can be caused by penetrating trauma but is almost always a consequence of sinusitis. Most commonly, the ethmoid sinus is involved in extension across the lamina papyracea. Blood cultures and complete blood counts (CBCs) should be done in all patients but do not reliably differentiate between the two conditions. Leukocytosis with left shift will be present in most patients with either condition. Bacteremia is infrequent but more common in young children. Cultures should be obtained from the eyelid, or any conjunctival or lacrimal sac discharge. Preseptal cellulitis occurs as a consequence of facial infection, trauma, insect bites, or a herpetic lesion. It also may occur as a result of bacteremia in children younger than 36 months. In this setting, prior to the introduction and routine use of conjugated *Haemophilus* vaccine, the most common pathogen was *Haemophilus influenzae* but it is now *Streptococcus pneumoniae*. The intact orbital septum usually prevents posterior spread of preseptal cellulitis in adults, but in children such spread can occur. Clinical evidence of trauma, insect bites, herpes infection, dacryocystitis, or sinus infection should be sought in all patients presenting with eyelid and periorbital inflammation.

Therapy

Oral antimicrobial coverage for *Staphylococcus aureus* and group A Streptococci is usually sufficient in uncomplicated cases of preseptal cellulitis in adults. Typical regimens include oral amoxicillin/clavulanic acid, a first-generation cephalosporin, or intramuscular ceftriaxone. Younger children should be admitted to the hospital and additionally receive antibiotic coverage for *S. pneumoniae* with an agent such as cefuroxime. Local prevalence of methicillin-resistant *S. aureus* and penicillin-resistant *S. pneumoniae* in the community should be considered in deciding initial antibiotic coverage pending the receipt of culture results. Lack of paranasal sinus disease, especially in children, lack of preceding periorbital trauma or antecedent lacrimal gland focus, and the presence of multiple orbital abscesses should suggest the possibility of MRSA orbital infection. Immediate surgical drainage of any focal abscess as well as appropriate empiric MRSA antibiotic coverage are recommended.⁴

An evidence-based literature review to determine whether children with simple preseptal periorbital cellulitis should be treated with IV or oral antibiotics failed to find

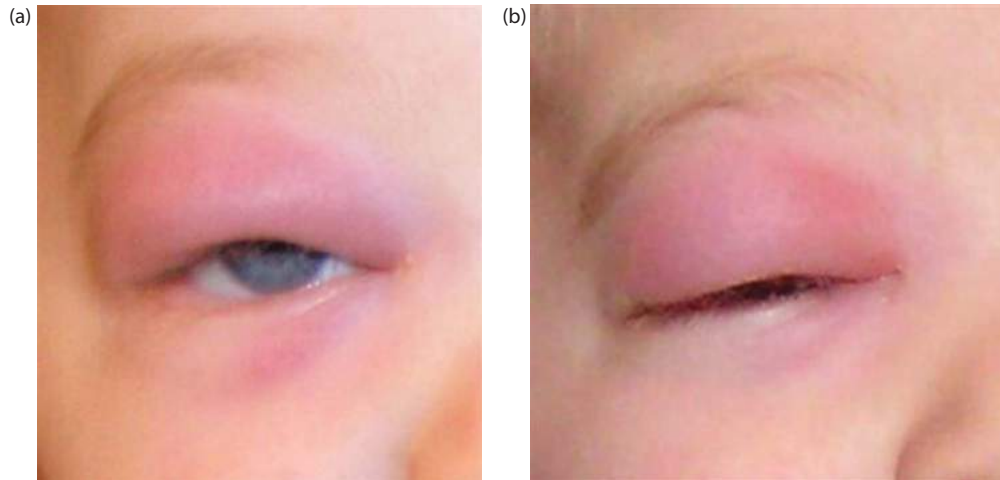


Figure 9.1 (a, b) Recurrent periorbital cellulitis in a young child. (Reprinted from the *International Journal of Pediatric Otorhinolaryngology*, 72, Kris R et al., 1577–1580, Copyright 2008, with permission from Elsevier.)

any evidence that either approach was superior.⁵ The authors noted that, in one hospital series, four pediatric patients with preseptal cellulitis developed intracranial, epidural abscess, or empyema.⁶ Suspected cases of orbital cellulitis should be admitted to the hospital for IV antibiotic treatment. Consultation with ophthalmology and otolaryngology should be obtained on an emergency basis. Following culture collection, antibiotic therapy should be initiated with coverage of *Streptococcus* species, *S. aureus*, anaerobes, nontypable *Hemophilus*, and *Moraxella catarrhalis*.

Course and Prognosis

Preseptal cellulitis usually has an excellent prognosis if recognized early and treated aggressively. Duration of therapy is dependent on response and extent of infection. If improvement does not occur in 24–48 hours, a resistant organism or orbital infection should be suspected and antibiotic coverage adjusted. Treatment should be continued for about 10 days. For orbital cellulitis, IV antibiotics should be continued until the infection is well controlled and consideration given to oral therapy to complete a course of 3–4 weeks. In a study of pediatric patients with orbital cellulitis, the need for surgery was associated with age older than 9 years, severe ocular pain, severe proptosis, and subperiosteal large abscess.⁷ Venous sinus thrombosis is a potential complication of orbital cellulitis as venous drainage of the orbit is through the cavernous sinus.

MALIGNANT EXTERNAL OTITIS

Background

Malignant (necrotizing) external otitis is an invasive infection of the external auditory canal and skull base most commonly occurring in elderly individuals with diabetes mellitus (86%–90%) and in patients with acquired immunodeficiency syndrome.^{8,9} The incidence of malignant otitis externa is rising, related to the increase in aging and diabetic populations.¹⁰ It is caused by *Pseudomonas aeruginosa* in more than 98% of cases though case reports have implicated other bacteria in some patients including *S. aureus*, *Proteus mirabilis*, and others. A high

index of suspicion for organisms other than pseudomonas, including MRSA, should be maintained in patients with signs and symptoms of malignant otitis externa, especially in those without diabetes.¹¹

Aspergillus fumigatus has been implicated in cases of fungal malignant external otitis. Occasional pediatric cases of malignant otitis externa have been reported, particularly in adolescents with diabetes and children with immune dysfunction as a result of leukemia, malnutrition, and/or solid tumors.¹² Children with the disease may display fever, leukocytosis, and pseudomonas bacteremia and develop facial nerve palsy more often than adults. Rare cases have been reported in infancy. Malignant external otitis may be complicated by facial nerve palsy, meningitis, brain abscess, and dural sinus thrombophlebitis and may be fatal.

Clinical and Laboratory Aids Required for Diagnosis

Patients with malignant otitis externa typically present with ear pain and drainage, and frequently they will have failed therapy with topical agents. This failure to respond to appropriate otitis externa treatment should raise a red flag and alert the clinician to consider strongly the diagnosis of malignant otitis externa.¹³ Patients may give a history of recent ear irrigation for impacted cerumen. Pain may extend to the temporomandibular joint and be exacerbated by chewing. A predisposing immunocompromising condition, diabetes most commonly, is usually present. On physical examination, granulation tissue is noted in the auditory canal at the bony cartilaginous junction.¹⁴ Drainage is present, but the tympanic membrane is usually undamaged.

In suspected cases, a negative CT scan does not necessarily rule out the diagnosis of malignant otitis externa.¹³ Nuclear medicine scans (technetium-99 or gallium-67) can aid diagnosis.¹³

Therapy

Following culture, therapy should be initiated with antibiotics covering *Pseudomonas* species. Until recently, oral therapy with ciprofloxacin 750 mg twice daily with or without the addition of rifampin has been advocated as the treatment of choice.^{15,16} Due

to increasing use of fluoroquinolones, resistance of *Pseudomonas* species to ciprofloxacin has been increasing with anywhere from 20% to 30% of isolates being reported as resistant.^{17–19} Hospital admission and IV antibiotic therapy with a third-generation cephalosporin, such as ceftazidime with anti-*Pseudomonas* activity is indicated, when there is a history of recent fluoroquinolone use, high community rates of ciprofloxacin-resistant *Pseudomonas*, or when clinical severity warrants close observation. Coverage for MRSA should be considered. The use of hyperbaric oxygen has been advocated to improve outcomes in malignant external otitis, but an analysis of published studies failed to find sufficient evidence in controlled studies for its use.²⁰

Course and Prognosis

Osteomyelitis of the skull base with involvement of vital structures is the most serious complication of malignant otitis externa.²¹ Cranial nerve neuropathy, especially of the facial nerve, may occur. The earliest series in the literature reporting on elderly diabetic patients with late-stage disease who underwent extensive surgery as primary therapy had a mortality rate of approximately 50%.²² Due to the high mortality with surgery, the use of synergistic combinations of semisynthetic penicillins and aminoglycosides was introduced to control pseudomonas; subsequently, third-generation cephalosporins, such as ceftazidime, were shown to have similar efficacy.^{23–25} Later, ciprofloxacin at a dosage of 1.5 g/d used over an average of 10 weeks showed superior efficacy with a reduction of mortality from approximately 30% to 2%–3%; however, this result was prior to recent increases in ciprofloxacin resistance.^{15,23} Premature termination of treatment may result in recurrence rates of 15%–20%.²⁶ Prolonged treatment is more likely to be associated with adverse drug reactions in patients receiving beta-lactam antibiotics than in those treated with ciprofloxacin.²⁷ In a recent study, facial nerve involvement previously cited as a poor prognostic indicator did not adversely affect survival.^{21,28}

MENINGOCOCCEMIA

Background

Meningococcemia, with or without meningitis, is one of the most serious emergencies in medicine. The causative organism, *Neisseria meningitidis*, has the ability to cause outbreaks, as well as sporadic cases of invasive meningococcal disease with devastating consequences often progressing rapidly to purpura fulminans, shock, and death. Large-scale outbreaks occurred in the United States in the 1940s associated with military deployments, but disease rates have remained relatively stable for the past 20 years, at 1–1.5 per 100,000 population.²⁹ Despite advances in treatment, approximately 10% of affected patients die from the disease, and another 10%–20% are left with severe sequelae such as hearing loss and limb amputation.³⁰ Affecting primarily the pediatric population, the highest rates of both meningitic and nonmeningitic meningococcal disease occur in infants younger than 1 year.³¹ Approximately one third of all cases of sporadic meningococcal disease occur in adults, and one half of these present without rash or meningitis.³² Recently cases of meningococcal infection have been reported in men-who-have-sex-with-men (MSM) and pilgrims attending the Hajj in Mecca.^{33,34} Given the high morbidity and mortality of meningococcal infections, rapid institution of antibiotic therapy and supportive care are paramount. Preadmission parenteral antibiotics (benzylpenicillin, ceftriaxone, and

chloramphenicol) have been suggested for patients presenting to a physician's office with signs of invasive meningococcal disease. Assuredly, no physician wants to miss the diagnosis of meningococcemia. The diagnosis of patients presenting with typical signs of acute meningitis is often straightforward. It is the patient who does not appear ill on initial presentation who represents a greater diagnostic challenge.³⁵ To not miss the diagnosis, it has been suggested that, in any acutely febrile patient, it is prudent to ask, "Why is this patient seeking help now?" and then "Could this patient have meningococcemia?"³⁵

Clinical and Laboratory Aids Required for Diagnosis

Early clinical clues to meningococcemia include a hemorrhagic (petechial or purpuric) rash; a blanching macular or maculopapular rash appearing in the first 24 hours; true rigors; severe pain in the extremities, neck, and back; vomiting; headache; and rapid evolution of illness.³⁵ The lesions of acute meningococcemia are indurated, gunmetal gray patches of purpura that display an irregular (infarctive) pattern (Figure 9.2). These may occur anywhere on the skin and can develop bullae and ulcerate (Figure 9.3) and progress to purpura fulminans (Figure 9.4). A transient blanching erythematous maculopapular eruption may arise before the appearance of purpura. In a study of children and adolescents with invasive meningococcal disease, the first classic sign to emerge was rash, which at the onset was nonspecific and only developed into a petechial (and then a largely hemorrhagic) eruption over several hours.³⁶ In this study, fever was the first symptom noted in children younger than 5 years. Headache was the first symptom in patients older than 5 years; 94% developed fever at some point, and irritability was a prominent symptom in younger children.³⁶ Three important features were identified as signs of early meningococcal disease in children and adolescents: leg pain, cold hands and feet, and abnormal skin color (pallor or mottling).³⁶ Eruption, meningismus, and impaired consciousness occurred later. In recent years, cases of retiform purpura and skin necrosis in adults that could be confused with purpura fulminans and meningococcemia have been associated with the use of cocaine



Figure 9.2 Child with meningococcal meningitis with retiform purpuric lesions. (Photo by Delso Calheiros, reproduced with permission from *Dermatology Atlas*: <http://www.atlasdermatologico.com.br/disease.jsf?diseaseId=287>.)



Figure 9.3 (a, b) Acute phase fulminant meningococcemia and purpura fulminans. (Reprinted from the *AORN Journal*, 97(5), Wick JM et al., 559–578, Copyright 2013, with permission from Elsevier.)



Figure 9.4 Purpura fulminans in an 88-year-old man with meningococcemia and multiorgan failure. Smear from skin revealed gram-negative diplococci. (Courtesy of Ronni Wolf MD.)

adulterated with levamisole. Typically patients do not appear septic though they have widespread dramatic necrotic lesions often involving the ears and nose.

Therapy

The prompt initiation of IV antibiotic therapy is essential in patients with suspected meningococcal disease. Third-generation

cephalosporins, such as cefotaxime or ceftriaxone, are the antibiotics of choice, if penicillin sensitivity testing is not available or is pending. Ceftriaxone, 100 mg/kg/d in one or two divided doses or cefotaxime, 200 mg/kg/d in three divided doses, may be used.^{37,38} Third generation cephalosporins are the antibiotics of choice if penicillin sensitivity is not available or is pending. Penicillin can be used once culture confirms sensitivity to penicillin but only if the MIC of the isolate is less than 0.1 micrograms/mL. Penicillin is dosed at 300,000 units per kg per day with a maximum of 24 million units per day.³⁷ Recently, intermediate resistance of some meningococci to penicillin has been reported from Europe. In a Portuguese study, one quarter (24.6%) of the isolates showed moderate resistance to penicillin.³⁹ A study from Scotland found an absence of “high-level” resistance to penicillin among meningococci and an 8.3% prevalence of moderate resistance.⁴⁰ Although there is some indication that a small number of strains in the United States display intermediate resistance to penicillin, the U.S. Centers for Disease Control and Prevention (CDC) has not recommended routine susceptibility testing of meningococcal isolates.⁴¹ Treatment of meningitis in children is aimed at the most likely pathogen based on epidemiologic information.⁴² Due to the significant prevalence of penicillin-resistant *S. pneumoniae*, empirical treatment of meningitis in children 1 month old or older should include vancomycin plus cefotaxime or ceftriaxone.⁴²

Course and Prognosis

In general, the mortality rate for meningococcal septicemia exceeds that of meningococcal meningitis. Reported mortality from meningococcemia ranges from 18% to 53%, whereas that of meningococcal meningitis has in the past 15–20 years

hovered around 10%.⁴³ Among adults with single episodes of community-acquired meningitis, risk factors for death included older age (≥ 60 years), obtunded mental state on admission, and seizures within the first 24 hours.⁴⁴ In a study of 3335 meningococcal deaths in the United States, 58% of deaths occurred among persons younger than 25 years. Mortality was increased in infants, young adults (15–24 years old), and older adults (older than 74 years).⁴⁵ Neurologic sequelae following meningococcal disease occur in 10%–20% of patients.⁴⁶ A number of treatment modalities have been used to improve the prognosis of meningococcal disease. There is controversy as to whether corticosteroids improve prognosis, but many groups use them routinely. A subgroup analysis of patients with meningococcal meningitis treated with corticosteroids showed a trend toward decreased mortality.⁴⁷

ROCKY MOUNTAIN SPOTTED FEVER

Background

RMSF is one of the most virulent human infections ever identified; 5%–10% of individuals infected die, and many others suffer sequelae, such as amputation, deafness, or permanent learning disability.⁴⁸ RMSF occurs throughout the continental United States, Canada, Mexico, Central America, and parts of South America. During the period 1997–2002, there were 2.2 cases per 1 million per year in the United States, and more than one half (56%) of cases were reported from only five states: North Carolina, South Carolina, Texas, Oklahoma, and Arkansas.⁴⁹ Although cases are reported throughout the year, most occur from May through January with a peak in July, August, and September (46% of 2298 cases in 2006).⁵⁰ During 2006, more than half of cases were reported from the South Atlantic region with 962 cases (42% of total U.S. cases) from North Carolina. Arkansas and Tennessee accounted for 13% and 11.5% of cases, respectively. Recently an increased incidence of RMSF on native American reservations in Arizona and in northern Mexico was related to brown dog tick (*Rhipicephalus sanguineus sensu lato*) exposure.⁵¹ The case fatality rate among young Native American children aged between 5 and 9 years was 11.5%.⁵¹ RMSF is most common in boys and men and Caucasians, and although children younger than 10 years were the group at highest risk in previous studies, in 2003 the highest age-specific incidence was in persons 40–64 years old.⁵²

Clinical and Laboratory Aids Required for Diagnosis

The initial symptoms of RMSF include sudden onset of fever, chills, and headache, associated with malaise and myalgias. Anorexia, nausea, vomiting, and photosensitivity are also commonly seen. Because the eruption may not be evident at the time a patient first presents for evaluation, clinicians should still maintain a high index of suspicion for the diagnosis in patients with a history of outdoor activities. History of a tick bite is elicited in only one half of patients with RMSF. Sixty to 70% of patients with RMSF present with the classic triad of fever (94%), headache (86%), and eruption (85%) 1–2 weeks after tick exposure⁵³; however, this occurs in only 3% of cases in the first 3 days of illness.⁵⁴ Temperature usually exceeds 38.9°C (102°F), and the majority of patients develop an eruption within 3–5 days following the onset of fever.⁵³ Children with RMSF present with fever (98%), eruption (97%), nausea and/or vomiting (73%), and headache (61%).⁵⁵ The eruption is maculopapular



Figure 9.5 Exanthem Rocky Mountain spotted fever. (Reprinted from the *Journal of the American Academy of Dermatology*, 49(3), McGinley-Smith DE et al., 363–392, Copyright 2003, with permission from Elsevier.)

before the appearance of petechiae and may be easily missed, especially in individuals with dark complexions.⁵⁶ Blanching erythematous macules, 1–5 mm in diameter, initially arise on the wrists and ankles (Figure 9.5) and spread to the palms and soles.⁵⁴ The eruption spreads centripetally to the arms, legs, and trunk. In 24–48 hours, petechiae and purpuric macules develop that may superficially resemble meningococcemia. Bilateral periorbital edema, suffusion of the conjunctivae, and edema of the hands and feet are highly suggestive of RMSF in the appropriate clinical setting. The severe headache (which patients may describe as the worst they have ever experienced) may mimic meningitis with meningismus in 18% of patients.^{53,54,57} The headache is usually frontal and is often associated with restlessness; severe myalgias of the abdomen, back, and legs; nausea; vomiting; and abdominal pain. Patients may display amnesia, psychiatric symptoms, and transient hearing loss.

CBC and a comprehensive metabolic panel should be done when considering rickettsial disease. White cell count in RMSF is usually normal, but increased numbers of immature band forms are often seen. Thrombocytopenia, mild elevations of hepatic transaminases, and hyponatremia also can occur. Blood cultures and examination of a peripheral smear are useful in ruling out other conditions that mimic RMSF. The presence of morula in the peripheral smear in either monocytes or granulocytes suggests human monocytic ehrlichiosis (HME) or human granulocytic anaplasmosis (HGA), respectively. Leukopenia with elevations of liver transaminases and thrombocytopenia further suggest HGA and HME. HGA is transmitted through the *Ixodes scapularis* tick, which does not transmit *Rickettsia rickettsii*, whereas HME is transmitted to humans through the lone star tick or *Amblyomma americanum* and possibly other tick species. Blood cultures are useful in assessing bacterial infections, particularly meningococcal infection, the early signs of which can be difficult to distinguish from RMSF. Cerebrospinal fluid in RMSF usually shows a pleocytosis (usually with <100 cells per milliliter) with neutrophilic or lymphocytic predominance. Protein is elevated, but glucose remains normal. Gram-negative diplococci with neutrophilic predominance and low glucose clearly favor meningococcal infection; however, there remains considerable overlap, and

empiric coverage for meningococcus is frequently unavoidable. Serologic testing and immunohistochemical or polymerase chain reaction (PCR) analysis of skin biopsy specimens can also confirm the diagnosis.

In a study of RMSF in children,⁵⁵ laboratory findings were nonspecific and similar to those that might occur, for example, in viral syndromes such that "no constellation of clinical and laboratory abnormalities has adequate sensitivity for their absence to exclude the diagnosis of RMSF in a child." Due to the rapid progression of infection, empiric therapy should not be withheld awaiting laboratory confirmation.

Treatment

Doxycycline is the drug of choice for treatment of both adults and children including infants with presumptive or proven RMSF.⁵⁸ Even though the use of tetracyclines in young children has been discouraged due to the potential for tooth discoloration, this effect is dose related and does not preclude the use of this agent.⁵⁹ One course of doxycycline in young children for presumed RMSF, a potentially life-threatening disease, has not been shown to cause clinically significant staining of permanent teeth.⁵² Doxycycline effectively treats ehrlichiosis, which may be confused with RMSF. Unfortunately, many practitioners are not aware that doxycycline is the preferred treatment in children. A survey of practitioners found that only 35% correctly chose doxycycline as the treatment of choice for RMSF in patients <8 years old.⁶⁰

Chloramphenicol is the preferred agent for treating RMSF occurring during pregnancy.⁶¹ Patients with RMSF should be admitted to the hospital and observed closely and treated for altered mental status or any organ dysfunction. Patients in more advanced stages of disease warrant admission to an intensive care unit for aggressive supportive measures.

Course and Prognosis

Appropriate treatment of patients with RMSF is often delayed for a number of reasons including lack of tick exposure history; occurrence of illness at times of year when tick activity is not at its peak; absence or delayed appearance of eruption; symptoms other than the classic triad of fever, eruption, and headache; and lack of headache.^{55,62–65} Of interest, presentation to a health-care provider early in the course of the disease has been associated with delay in the initiation of specific antirickettsial therapy.^{55,65} For example, in one study by Buckingham, 48 children were seen by medical providers after a median of 2 days of symptoms but did not receive specific antirickettsial treatment until after a median of 7 days of symptoms. In fact, two of the three children who died in that study, although seen early on, were not given appropriate treatment. Also in that study, more than one third of patients spent time in an intensive care unit, 16% received mechanical ventilation, and 17% received pressors. Before the introduction of effective antirickettsial agents, 13% of children with RMSF died.⁶⁶ Despite the availability of specific therapy and improved supportive medical care, the case fatality rate in children younger than 10 years is still 2%–3%.

Several clinical and laboratory variables have been associated with fatal outcome including increased age; male sex; neurological involvement; elevated levels of creatinine, aspartate aminotransferase, and bilirubin; decreased levels of serum sodium; and decreased platelet count.⁶⁷ The development of

acute renal failure increased the odds ratio of dying 17-fold in one study.⁶⁷ The presence of a deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD) may portend a more fulminant course due to the development of hemolysis.⁶⁸ Even with recovery, patients may suffer ongoing neuromotor impairment at the time of discharge from the hospital; this impairment may persist in some patients,⁶⁹ particularly if neurologic compromise, especially coma, occurs during the acute phase of the illness. Persistent sequelae include dysarthria, difficulty reading, impaired memory, deafness, and paresthesias. Gangrene can necessitate amputation of digits or entire extremities.

MEDITERRANEAN SPOTTED FEVER Background

Mediterranean fever (Boutonneuse fever) has been described in many countries under a variety of names. It is caused by *Rickettsia conorii* and its subspecies, and the vector is the brown dog tick *Rhipicephalus sanguineus*. Although usually a benign, uncomplicated disease with recovery the norm, it may sometimes be severe and fatal.⁷⁰ Life-threatening complications reported in travellers to endemic areas have been diverse including meningitis, encephalitis, pulmonary involvement, septic shock, and multiorgan failure,⁷¹ so clinicians must maintain a high level of clinical suspicion when presented with a traveller returning from Southern Europe or Africa with fever and skin rash or with fever and eschar(s).

The mortality rate is usually estimated at approximately 2.5%, but a fatality rate of up to 5.6% has been reported in affected hospitalized patients in Israel, France, and Portugal.⁷² The disease tends to be more severe in the elderly population and in patients with cirrhosis, chronic alcoholism, and G6PD deficiency.⁷³ In Beja, a Portuguese southern district, a case fatality rate of 32.3% was reported in hospitalized patients with Mediterranean spotted fever.⁷⁴ The risk of dying was associated with diabetes, uremia, vomiting, and dehydration. A subspecies of *R. conorii* (*israelensis*), the cause of Israeli spotted fever, has been isolated from patients in Sicily and Portugal and may be associated with more severe disease. The disease has been reported throughout the Mediterranean basin, sub-Saharan Africa, India, around the Black Sea, and in the eastern part of Russia close to Japan. Diagnosis peaks in August in endemic areas of France and Spain suggesting that larvae and nymph forms are important in disease spread. The peak activity of adult ticks occurs several months earlier during the spring. Reports of Mediterranean spotted fever throughout the year and from colder areas removed from the Mediterranean imply that *R. sanguineus* can survive in the microclimates of homes and kennels.

Clinical and Laboratory Aids Required for Diagnosis

The incubation period of Mediterranean spotted fever is approximately 7 days. Disease onset is abrupt and typically begins with high fever, flu-like symptoms, a black eschar (*tache noire*) at the site of the tick bite, and a maculopapular eruption. The *tache noire* is said to be present in approximately 74% of cases but is uncommon in the Israeli form. Eruption is described as maculopapular but may be purpuric in 10% of cases.

Laboratory studies are often nonspecific with thrombocytopenia, leukocyte count abnormalities, both lymphopenia

and leukocytosis, and elevated hepatic enzyme levels. Early diagnosis of Mediterranean spotted fever can be achieved using immunofluorescence or immunohistochemical studies of skin biopsy material or by PCR.^{75,76} Both techniques require experienced personnel and may have limited availability. Serologic studies provide retrospective confirmation of the diagnosis. Antibodies to rickettsiae may not be detectable until 7–10 days after infection is clinically apparent. An acute blood sample should be collected early in the course of the disease, and a second specimen should be obtained 2 weeks later. If a fourfold increase in antibody titer is not observed, collection of a third sample after 4–6 weeks should be considered. Specific diagnosis may not be made until the patient has recovered or died.

Treatment

Treatment should be initiated as soon as the diagnosis is suspected. Doxycycline is the drug of choice and is given for a 7-day course of therapy or until the patient is afebrile for 3 days. Doxycycline has been shown to effectively treat Mediterranean spotted fever with a 1-day course of therapy.⁷⁷ Doxycycline is contraindicated in pregnancy and not usually recommended for use in children younger than 8 years with the exception of patients with RMSF. Chloramphenicol is also an effective antibiotic agent and had previously been used in pregnancy. Aplastic anemia occurs in 10 of 40,000 patients treated with chloramphenicol, and gray baby syndrome (comprising abdominal distension, pallor, cyanosis, and vasomotor collapse usually leading to death) has been described in neonates treated with this drug. Although there has been no report of an infant exposed in utero having developed gray baby syndrome or aplastic anemia, few obstetricians and pediatricians are comfortable with its prescription. In vitro studies of clarithromycin and azithromycin have suggested effectiveness of these antibiotics in treatment of *R. conorii* infection. Clinical trials suggest that these agents provide a safe and effective alternative for treatment of children younger than 8 years with Mediterranean spotted fever.^{78,79} Fluoroquinolones also have been shown in vitro to be effective against *R. conorii*, but some authors have presented data suggesting that the use of fluoroquinolones is associated with more severe disease and longer hospital stays.^{80,81}

Course and Prognosis

In general, Mediterranean spotted fever has a good prognosis, if appropriately treated. Risk factors for more severe disease include diabetes, G6PD deficiency, older age, cirrhosis, and alcoholism. Delay in initiation of appropriate antibiotic coverage is also frequently cited as a risk factor for poor prognosis; however, a retrospective study in the Beja district of southern Portugal,⁷⁵ which experienced a 32.3% case fatality rate for hospitalized patients in 1997, did not bear this out. Diabetes, vomiting, volume depletion, and uremia were significantly correlated with risk of dying. Treatment of severe illness induced by *R. conorii* may require more than chemotherapeutic elimination of the etiologic agent. The multiorgan manifestations of endothelial damage and increased vascular permeability may necessitate admission to an intensive care unit for monitoring of central pressures and airway management. Additional antibiotic coverage may be required to cover bacterial leakage from a compromised gut or from aspiration.

ANTHRAX Background

Anthrax is primarily a disease of wild and domestic animals (cattle, sheep, and goats) caused by the spore-forming bacterium *Bacillus anthracis*. Human disease results from exposure to infected animals or tissue from infected animals. Infection occurs after cutaneous inoculation or inhalation of spores or after ingestion of infected material. *B. anthracis* can exist as a stable spore form for years and can be weaponized as a bioterrorism agent such as what occurred in the United States in 2001 when powder containing anthrax was placed in letters and disseminated via the U.S. Postal Service. Although the cutaneous form of anthrax is usually considered the least severe presentation, it can result in fatality if not adequately treated. A rare complication, malignant edema, is characterized by severe edema, induration, multiple bullae, and shock.⁸² Involvement of the face, neck, and chest may require intubation and corticosteroids to prevent asphyxiation. In a series of 28 cases of cutaneous anthrax reported in 2003 from Turkey, two patients (8%) died from anthrax sepsis.⁸³ A study from the Artibonite Valley of Haiti reported 87 cases of cutaneous anthrax over a 4-year period.⁸⁴ Seven of 87 patients (8%) died, 4 from asphyxiation after facial and neck edema compressed the trachea causing airway obstruction. Two patients died of symptoms associated with concurrent gastrointestinal anthrax. Anthrax can cause a severe, usually fatal meningoencephalitis from both the cutaneous and inhalational routes.^{82,85}

Clinical and Laboratory Aids Required for Diagnosis

The diagnosis of anthrax is usually straightforward when it occurs in a typical occupational or environmental setting involving exposure to infected animals or contaminated animal products, such as hides, wool, hair, or ivory tusks.⁸⁶ In the past, urban cases of anthrax were usually associated with imported products such as shaving brushes, and more recently two cases were reported in Connecticut in a drum maker and his child after exposure to contaminated goat hides imported from Guinea.^{87–89}

The primary lesion of cutaneous anthrax is a painless papule that usually develops approximately 7 days (range = 1–12 days) after inoculation of infected material.⁹⁰ It most commonly occurs on the head, neck, or arms and develops a central vesicle or bulla that becomes hemorrhagic as the lesion enlarges. The classic black central eschar is often surrounded by erythema and sometimes extreme edema (Figure 9.6). The presence of a primary pustular lesion should suggest another diagnosis. Multiple lesions sometimes occur, and there may be tender regional lymphadenopathy and systemic symptoms of fever, chills, and fatigue.⁹⁰ Anthrax may occur on the eyelid and be associated with preseptal cellulitis, and severe edema resulting from a primary lesion on the neck (bull neck) may result in asphyxiation (Figure 9.7).^{84,91} Cutaneous anthrax should be differentiated from insect bites, brown recluse spider bite (almost always painful), tularemia, the *tache noire* of rickettsial diseases, cat scratch disease, ecthyma gangrenosum, orf, and staphylococcal or streptococcal ecthyma. When dealing with a patient with suspected cutaneous anthrax, universal precautions should be followed. The American Academy of Dermatology recommendations include swabbing exudates using a Dacron- or rayon-tipped swab (cotton should not be used) to obtain material for Gram stain and culture.⁹⁰ Vesicular fluid is optimal



Figure 9.6 Cutaneous anthrax in a 7-month-old infant. Progression of lesions: (a) hospital day 5, (b) hospital day 12, (c) 2 months after discharge. (Reprinted from Freedman, A. et al. *JAMA*, 287(7), 869–874, 2002, with permission. Copyright 2002, American Medical Association. All rights reserved.)



Figure 9.7 Facial cutaneous anthrax with massive edema. (Used with permission, *Am J Trop Med Hyg*, 2007;77:806–811.)

for isolation of the organism. If only an eschar is present, the edge should be lifted and swabs inserted to obtain fluid. Two skin biopsies are advocated, one for histological examination including special stains and immunohistochemistry and the other for culture.⁹² Treatment should be instituted while awaiting results. Serology and PCR assay may be available through governmental agencies such as the CDC.⁹³

Treatment

Uncomplicated localized cutaneous anthrax should be treated with oral ciprofloxacin 500 mg twice daily or doxycycline 100 mg twice daily.⁹⁴ The usual duration of treatment is 7–10 days, but in the context of a bioterrorism attack, the CDC recommends a 60-day course of treatment due to the increased likelihood of exposure to aerosolized anthrax. For children, the CDC recommends oral ciprofloxacin 10–15 mg/kg every 12 hours, not to exceed 1 g/d, or doxycycline. For children up to 8 years old (or those older than 8 years weighing <45 kg), the CDC recommends a doxycycline dosage of 2.2 mg/kg every

12 hours. The dosage of doxycycline for children older than 8 years and weighing at least 45 kg is 100 mg every 12 hours. The CDC has also recommended the use of ciprofloxacin and doxycycline in pregnant woman, although these agents traditionally have been avoided in pregnancy.

Cutaneous anthrax, occurring on the head and neck and in cases with systemic involvement or severe edema, should be treated with the IV antibiotic regimens recommended for inhalational anthrax. A multidrug regimen is recommended in suspected cases of bioterrorism, because antibiotic resistance may have been engineered into weaponized anthrax. The initial treatment protocol recommended for inhalational bioterrorism-associated anthrax is ciprofloxacin 400 mg IV every 12 hours or IV doxycycline 100 mg every 12 hours plus one or two additional agents. IV therapy can be switched to oral treatment when clinically warranted. Additional agents that have activity against *B. anthracis* include penicillin, ampicillin, imipenem, clindamycin, clarithromycin, rifampin, chloramphenicol, and vancomycin. Inhalational anthrax and severe cutaneous disease in children are treated with IV ciprofloxacin 10–15 mg/kg every 12 hours (not to exceed 1 g/d in children) or IV doxycycline. Children younger than 8 years and those 8 years old or older but who weigh less than 45 kg are treated with IV doxycycline 100 mg every 12 hours. One or two additional antibiotics are added to this regimen in this protocol.

Course and Prognosis

Prognosis of anthrax depends on the type of exposure. Many sources quote a mortality rate of up to 20% in untreated cutaneous anthrax, 25%–75% for gastrointestinal anthrax, and 80% or more for inhalational anthrax. In one series, four patients (5.6% of patients) with cutaneous anthrax progressed to septicemia and shock.⁹⁵ Fulminant inhalational anthrax is usually fatal, but initiation of antibiotics or anthrax antiserum therapy during the prodromal phase can improve survival.⁹⁶

TULAREMIA Background

Tularemia is a zoonotic disease with worldwide distribution caused by *Francisella tularensis*, a fastidious, gram-negative bacteria.^{97,98} It has been speculated that tularemia was the cause

of the biblical plague of the Philistines.⁹⁹ The Old Testament warns in Leviticus 11:6, "And the hare, because she cheweth the cud but parteth not the hoof, she is unclean unto you."¹⁰⁰ Transmission to humans occurs by several mechanisms, most commonly direct or indirect inoculation of the skin from infected animal tissues, body fluids, or pelts.¹⁰¹ The animals implicated in transmission of tularemia vary with the geographic area. In the United States, jackrabbits, cottontail rabbits, beavers, muskrats, meadow voles, and sheep are usually implicated. The disease may also be spread by arthropod vectors, such as deerflies, mosquitoes, and several varieties of ticks. Spread to humans can also occur from drinking contaminated water or breathing contaminated dirt or aerosol.¹⁰² Interest in tularemia has been heightened in recent years due to its potential for use as an agent of bioterrorism. The organism is highly virulent in susceptible hosts. A low infectious dose of 10–50 organisms can establish infection in an open wound or if aerosolized and inhaled. The two subspecies of *F. tularensis* commonly associated with human disease are *F. tularensis* subsp. *tularensis* and *F. tularensis* subsp. *holarctica*. The *tularensis* subspecies is found only in North America and is the more virulent of the two. The type of disease that develops reflects the route of infection. Ulceroglandular disease, the most common presentation, follows exposure of broken skin to contaminated animal material and occurs on the upper extremities in more than 75% of patients.¹⁰³ Lesions on the lower extremities, abdomen, back, or head usually result from exposure to ticks or deerflies.

Clinical and Laboratory Aids Required for Diagnosis

Dermatologists are most likely to encounter patients with ulceroglandular, glandular, or perhaps oculoglandular tularemia. A typical patient will present with the abrupt onset of fever, chills, malaise, and fatigue after an incubation period of 1–10 days (average of 3 days).¹⁰² The most common presenting complaint is of enlarged, tender, localized lymphadenopathy with overlying erythema. The initial skin lesion may be present at the time of presentation or shortly thereafter and is a painful, red papule that undergoes necrosis leaving a tender ulcer with a raised border (Figure 9.8).¹⁰⁴ Cutaneous ulcers range in size from 0.4 to 3 cm and are usually solitary.



Figure 9.8 Tularemia—cutaneous ulcer. (From Oyston, P.C.F. et al., *Nat Rev Microbiol*, 2004;2:967–968.)

Multiple lesions can sometimes occur and are usually caused by exposure to more than one animal.¹⁰³ The primary lesion may evolve over the course of the disease. In a Swedish study, primary lesions were described as "encrusted" in one third of cases and "ulcerous" or "pustular" each in about 20% of cases. "Papular" primary lesions were noted in 13% and "macular" or "vesicular" lesions each occurred in approximately 3%–4% of cases. Indeed, cases of tularemia have been initially misdiagnosed as herpes simplex or herpes zoster infection.¹⁰⁵ A recent case report describes a 38-year-old microbiologist with pneumonic tularemia who presented with a vesicular eruption and erythema nodosum.¹⁰⁶

Secondary skin eruptions including erythema nodosum have been reported in patients with tularemia. In the previously mentioned Swedish study, almost 30% of patients displayed a secondary skin eruption apart from any primary lesions or erythema overlying enlarged lymph nodes. Such eruptions were most commonly papular or maculopapular. Erythema nodosum occurred in 3% of patients, all girls and women. In a recent study from Turkey, erythema multiforme was found in 11.3% of patients, most of whom presented with the oropharyngeal and glandular forms; ulcer was found in (6%), urticaria in (3.3%), erythema nodosum in (2.6%), and cellulitis in (0.7%).¹⁰⁷

Suppuration of involved lymph nodes may occur. In glandular disease, lymphadenopathy occurs in the absence of a primary lesion. Ulceroglandular tularemia must be differentiated from other causes of ulceroglandular disease including *Bartonella henselae* (cat scratch fever), *Yersinia pestis* (plague), *Spirillum minus* (spirillary rat bite fever), and other bacterial adenitis. Other diagnostic considerations are anthrax, herpes simplex, chancroid, syphilis, and mycobacterial disease.¹⁰⁸ Oculoglandular disease resulting from direct or indirect exposure of the conjunctivae to infectious material presents with conjunctivitis, chemosis, lacrimation, photosensitivity, lid edema, and conjunctival ulceration accompanied by tender lymphadenopathy in the preauricular, submandibular, and cervical regions. Pharyngeal disease occurs when the primary exposure is within the oral cavity with contaminated foods or water. Typhoidal tularemia is distinct from the other forms in that it is not accompanied by adenopathy and the portal of entry may not be identifiable. This form usually affects persons with some degree of immune compromise and may have a rapid and fulminant course. A pneumonic form also exists in which the pulmonary findings are the most prominent feature. Tularemia should be suspected when typical clinical findings occur in a patient with an occupational or recreational exposure to animals in an endemic area. Diagnosis outside of an endemic area requires a high index of suspicion.¹⁰⁸ The incubation period is usually approximately 3–5 days, and onset of disease is often abrupt. Fever, chills, malaise, sore throat, and headache are frequent, and pulse-temperature dissociation may occur in 42% of cases. Persistent fever, greater than 101°F, is common over the course of several days. Routine laboratory testing is nonspecific. Leukocytosis may or may not be present. Thrombocytopenia, elevation of transaminases and creatine kinase, and myoglobinuria may also be present. The organism can be isolated from wound drainage, lymph aspirates, sputum, and blood. Stringent precautions should be taken when handling specimens to prevent transmission of infection to hospital and laboratory personnel. *Francisella* is a biosafety level 3 pathogen, and the laboratory should be warned if it is suspected. Relay of specimens to government health departments

for processing may be the best option for both expertise in culture and availability of PCR or fluorescent antibody testing. Confirmation of infection is usually made with increasing titers of antibodies in acute and convalescent sera.

Treatment

Streptomycin is the preferred drug for treatment of tularemia. Because it may not be readily available, gentamicin is commonly used with good results. Beta-lactam antibiotics and macrolides are not effective and should not be used. Fluoroquinolones provide effective coverage, as do tetracyclines. A study from Spain showed ciprofloxacin to be superior to both streptomycin and doxycycline in that it had the lowest percentage of primary treatment failures; however, this study was nonrandomized and retrospective. If the condition of the patient merits hospitalization, IV therapy with streptomycin or gentamicin is indicated. Stable patients may be treated with oral antibiotics with ciprofloxacin or doxycycline, with ciprofloxacin being the preferred oral agent for confirmed tularemia.

Course and Prognosis

Suppuration of large or flocculent lymph nodes is a common complication. Large nodes should be aspirated to prevent this complication. Another possible sequel to infection with tularemia is a prolonged period of fatigue that may persist several weeks even following adequate antibiotic treatment. Prior to the introduction of streptomycin in the 1950s, patients often suffered from lingering symptoms, and the case mortality for ulceroglandular disease was about 5%.¹⁰⁹ Death rates from all forms of tularemia in the antibiotic era are about 4% but were as high as 33% prior to the use of streptomycin.¹⁰⁴

V. VULNIFICUS INFECTION

Background

V. vulnificus is not only the most virulent food-borne pathogen in the United States but is a source of invasive, potentially life-threatening wound infections.¹¹⁰ Most cases in the United States occur in individuals with cirrhosis who eat undercooked oysters from the Gulf of Mexico, but cases of *V. vulnificus* have been reported from Japan, Taiwan, Korea, Brazil, Mexico, Germany (from the Baltic Sea), Denmark, Spain, Israel, and Australia.^{111–121} A severe outbreak occurred in Israel in fish market workers from handling infected tilapia.¹²⁰ *V. vulnificus* is present in shallow sea and estuarial waters especially during the warm summer months. The gram-negative, comma-shaped organism is found in oysters, crustaceans, and shellfish.¹¹² The main risk factors for developing *V. vulnificus* infection are consumption of raw or inadequately cooked oysters or shellfish, exposure of a preexisting open wound to contaminated seawater, injury to the skin while in contact with infected water, and handling contaminated marine species (as in fish handlers). Wound infections are most likely serious in persons with underlying chronic liver disease or other predisposing factors who engage in water recreational activities. Also at risk are victims of natural disasters such as tsunamis and flooding after hurricanes. Eighteen wound-associated *Vibrio* cases were reported in several states in victims of Hurricane Katrina of which 14 (82%) were *V. vulnificus* and three were *V. parahaemolyticus*. Five (28%) patients with wound-associated *Vibrio* infections

died, three from *V. vulnificus* and two from *V. parahaemolyticus*. Because early, specific antibiotic therapy, aggressive wound management, and supportive measures can reduce mortality, it is incumbent upon physicians to be familiar with the recognition of *V. vulnificus* infection.

Clinical and Laboratory Aids Required for Diagnosis

Infection with *V. vulnificus* should be suspected in any patient presenting with cellulitis or sepsis after exposure to brackish or salt water or with a history of recent ingestion of raw or undercooked seafood, mainly raw oysters. The presence of hemorrhagic bullae complicating cellulitis in a patient with a history of liver disease or diabetes should further suggest the diagnosis (Figure 9.9).¹²² A small study comparing the clinical aspects of necrotizing fasciitis caused by *Vibrio* compared to that caused by streptococci pointed out several significant differences. All cases of *Vibrio* infection occurred during summer months in patients with underlying chronic liver dysfunction and were probably caused by raw seafood consumption.¹²³ In this study, *Streptococcus*-induced necrotizing fasciitis occurred in winter, and only one patient had chronic liver disease. In patients with *Vibrio*-induced disease, edema and subcutaneous bleeding (ecchymosis and purpura) were seen early on, but cutaneous necrosis did not occur. In patients with streptococcal disease, subcutaneous bleeding was rare and necrosis was common. Blood and wound cultures should be obtained immediately in all patients with suspected *Vibrio* infection. Gram stain of exudative material may suggest the pathogen and reinforce clinical suspicion. Progression of infection can be rapid and fulminant, so that expediency in workup and prompt initiation of antibiotic therapy are essential. Soft-tissue infection with *V. vulnificus* has a propensity to rapidly progress to necrotizing fasciitis. Clinical findings may include edema, patchiness, erythema, and tenderness. Hemorrhagic bullae or compartment syndrome may already be apparent at the time of presentation.



Figure 9.9 *Vibrio vulnificus* infection with hemorrhagic cellulitis. Inset: Gram-negative rods seen on Gram stain. (Printed with permission from Falcon, L.M. et al., *N Eng J Med*, 2005;353:1604.)

Treatment

Prompt initiation of antibiotic therapy and surgical debridement are the cornerstones in the management of *Vibrio* infections. When there is suspicion of this pathogen, antibiotic treatment should be started with a third-generation cephalosporin and a tetracycline. The combination of third-generation cephalosporins, commonly ceftriaxone or ceftazidime, with tetracycline, minocycline, or doxycycline have shown synergy. Recent studies with fluoroquinolones have shown these agents to be as effective as the cephalosporin-tetracycline combination in vitro and in murine models. A study of surveillance data suggests that inclusion of a fluoroquinolone is associated with decreased mortality.¹²⁴ Due to the rarity of the infection, it is unlikely that a blinded clinical trial will ever be carried out. Surgical consultation should be obtained and appropriate debridement of necrotic tissue done on an emergency basis. Fasciotomy may be needed, and if infection has progressed amputation may be required to remove the devitalized limb and control systemic sepsis.

Course and Prognosis

Prognosis is significantly better with early intervention and timely initiation of antibiotic coverage. Patients in whom the severity of infection is not immediately recognized or in those who present later in the course of infection do not fare as well. Overall, 40% of *V. vulnificus* infections are fatal, with case fatality rates of approximately 50% from primary septicemia and 15%–20% for wound infections.^{125,126} Persons most at risk are those with chronic alcoholic liver disease, hepatitis B or C, hemochromatosis, renal insufficiency, or adrenal insufficiency.¹¹²

HYDROPHILA INFECTION

Background

Aeromonas species are gram-negative rods usually found in fresh or brackish water and soil, which also have been isolated from chlorinated drinking water and even from hospital water supplies.^{127,128} They cause disease in fish and other cold-blooded aquatic animals, mammalian species, and humans.¹²⁹ Human infection occurs through contact with contaminated fresh or brackish water and soil and can give rise to cellulitis within 8–48 hours. It may also present as an isolated abscess that may lead to sepsis.¹³⁰ *A. hydrophila* is the species most commonly associated with soft-tissue infection. The clinical presentation is similar to that of *V. vulnificus* soft-tissue infection and similarly gives rise to sepsis primarily in patients with underlying cirrhosis or malignancy.¹³¹ *Vibrio* infections are associated with higher WBC count and AST, and more bacteremia and hemorrhagic bullae than *Aeromonas* infections.¹³²

Clinical and Laboratory Aids Required for Diagnosis

The most important clue suggesting *A. hydrophila* infection is a history of soft-tissue injury associated with exposure to freshwater or soil. Posttraumatic wound infections caused by *Aeromonas* may be clinically indistinguishable from cellulitis due to *Streptococcus pyogenes* or *S. aureus*, so that limiting empiric therapy to these organisms will likely miss the pathogen. Infection with *A. hydrophila* occurs in a variety of settings. In recreational activities involving freshwater (such as boating, swimming, or wading), abrasions or lacerations

may become infected, and in commercial situations (such as in fisheries), wounds may be exposed to contaminated freshwater. Infections of burns with *Aeromonas* have been reported after submersion or dousing of the injured part with water and after rolling the victim in soil to extinguish flames. Motor vehicle, machinery, or boating accidents may also expose people to wound contamination with *Aeromonas* in a culture bed of devitalized tissue. Although *Aeromonas* bacterial counts are often similar in marine environments to those in freshwater, infection from seawater, for some unknown reason, usually does not occur. *Aeromonas* cellulitis also may develop in skin grafts or flaps in which leeches were utilized to relieve venous congestion.¹³³ *Aeromonas* species are resident flora in the foregut of leeches aiding them in the digestion of heme. Cases of leech-related ciprofloxacin-resistant *Aeromonas* infections have been reported that required treatment with ceftriaxone.^{134–136}

Initial evaluation should include Gram stain of exudates or aspirates and bacterial culture. Depending on the extent of the disease, leukocytosis and fever may be present. In a study of a community outbreak of *Aeromonas* cellulitis following a mud football tournament, 26 cases of soft-tissue infection were cataloged with 22 of 26 persons presenting with nonlesional symptoms including eruption, malaise, fever, rigors, headache, nausea, sore throat, or earache. Some authors make note of an odd fishy or sweet, sickly, foul odor.^{137,138}

Therapy

A combination of surgical and medical therapy is most often required. The tendency of *Aeromonas* to form subcutaneous abscesses may not be clinically apparent, and early surgical consultation is advised.¹³⁷ Incision and drainage may be curative in some cases. The *Aeromonas* species are β -lactamase producers and are often resistant to penicillin, ampicillin, carbenicillin, first-generation cephalosporins, ticarcillin, vancomycin, and clindamycin.¹³⁸ Susceptibility to piperacillin, ticarcillin-clavulanate, and tetracyclines is variable. Fluoroquinolones and trimethoprim-sulfamethoxazole are usually effective, but reports of decreasing susceptibility of strains emphasize the need for close follow-up of response to therapy and adjustment antimicrobial therapy based on microbiological sensitivity testing.

Course and Prognosis

Aeromonas infection has a guarded prognosis. Bacteremia and septicemia are more common in patients with underlying cirrhosis and malignancy and portend a worse outcome. In contrast, cases of septicemia have been reported in otherwise healthy individuals.¹³⁹ In a study from Taiwan, the crude fatality rate of monomicrobial *Aeromonas* bacteremia was 30% within 2 weeks after the onset of infection.¹³¹ Some patients with myonecrosis from *Aeromonas* infection require limb amputation.¹⁴⁰

CHROMOBACTERIUM VIOLACEUM INFECTION

Background

C. violaceum is a gram-negative rod that occurs as a ubiquitous saprophyte of soil and water in tropical and subtropical areas.¹⁴¹ It is an uncommon pathogen in humans (<150 cases in the literature) but has a high fatality rate. Cases have been reported from Asia, Australia, Africa, the United States, and South

America.^{141,142} Most cases in the United States are reported from Florida. Human infection usually begins with cellulitis and skin abscesses that rapidly progress to sepsis and abscesses of internal organs. U.S. cases have been related to wading in pools of rainwater or muddy ditches, walking barefoot, following trauma, and swimming in freshwater.¹⁴³

Clinical and Laboratory Aids Required for Diagnosis

C. violaceum infection can be rapidly fatal. The most crucial factor determining survival is the recognition that the bacterium may be present and to cover for it empirically. The infection is found in tropical and subtropical regions and usually occurs in the summer months. There is a predilection for patients with chronic granulomatous disease, deficiency of polymorphonuclear leukocyte G6PD, and neutrophil dysfunction; however, fulminant disease has been reported repeatedly in patients with no apparent immune dysfunction.¹⁴⁴ Localized infection with regional lymphadenopathy occurs after contamination of damaged skin exposed to soil or stagnant water. Systemic infection can occur following aspiration or ingestion of contaminated material. The usual presentation is with fever, hepatic abscess, and skin lesions, although preseptal and orbital cellulitis has been reported as well as osteomyelitis, meningitis, and brain abscess. Skin lesions may consist of multiple nodules, hemorrhagic and pustular blebs with surrounding erythema, abscesses, cellulitis, and purpura scattered over the face, body, and extremities.^{145,146} The palms and soles may be affected. Ecthyma gangrenosum also has been reported.¹⁴⁷ Leukocytosis with left shift may be the only laboratory abnormality. Liver enzymes, platelet counts, and sedimentation rates may or may not be abnormal early in the course of infection. Culture of the organism confirms the diagnosis. Material from wound drainage, blood, conjunctival exudates, and abscess drainage or aspirant should immediately be sent for culture and susceptibility testing. *C. violaceum* is generally known to be resistant to first-generation cephalosporins and penicillins. Third-generation cephalosporins, ureidopenicillins, tetracyclines, and aminoglycosides have demonstrated mixed effectiveness. The organism is generally sensitive to trimethoprim-sulfamethoxazole, gentamicin, ciprofloxacin, and imipenem. Before 1990, *C. violaceum* infection was usually treated with chloramphenicol, trimethoprim-sulfamethoxazole, tetracycline, or aminoglycosides; however, several new agents introduced after 1990, including fluoroquinolone and carbapenem, have demonstrated good activity against this microorganism.¹⁴⁸ The frequency of hepatic abscess formation has prompted some authors to advocate ultrasound examination of the liver and spleen in all persons from whom *C. violaceum* has been cultured followed by surgical drainage of any abscesses visualized.

Course and Prognosis

Anyone found to be infected with *C. violaceum* should be evaluated for underlying immunodeficiency.¹⁴⁷ IV antibiotic therapy should be continued until all foci of infection have been cleared. As the organism has been known to recur following apparent resolution of infection, consideration of an extended course of oral antibiotic therapy is appropriate. Survival is dependent on the early recognition of the infection with initiation of effective antibiotic therapy. Recognition of the potential of this organism to form abscesses in multiple sites is important. The fatality rate of all cases with known outcome was 65% in 1998. Improvements in antibiotics and medical management

have decreased the fatality rate of 81% (from 1937 through 1979) to 41% (from 1980 to 1994).¹⁴³ Under the best of circumstances, the prognosis with this infection remains guarded.

CONCLUSIONS

We have described the clinical presentation and treatment of several infections with which the dermatologist and other specialists should be familiar. Most of these are relatively uncommon so physicians may not include them in their differential diagnoses. For that reason, knowledge of their often dramatic clinical presentations is essential as it will allow early diagnosis and the initiation of prompt therapy, which may be lifesaving.

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Bacteremia, sepsis, septic shock, and toxic shock syndrome

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In the emergency department, intensive care unit, and primary care setting, dermatologic conditions rank as one of the most common disease presentations. It is often a challenge for physicians to differentiate routine skin ailments from more serious, life-threatening conditions that require immediate intervention. This chapter highlights some dermatologic emergencies that plague physicians daily and initially may present with cutaneous manifestations. Septic shock and toxic shock syndrome (TSS) are potentially fatal medical emergencies that manifest with dermatologic signs, making a good understanding of dermatology a crucial step in rapid and early diagnosis of these two emergencies. As part of a clinical continuum, the terms *bacteremia*, *sepsis*, and *septic shock* have for many years been confused due to the inaccurate usage of terminology associated with such infections. In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine convened a Consensus Conference to standardize terminology and provide a framework for physicians to accurately identify the body's systemic response to infection. These quantifiable definitions work on a clinical continuum established by clinical and laboratory findings. Attempts to improve the accuracy of these 1992 guidelines have met with mixed success. In selected conditions (e.g., pneumonia) other prognostic tools such as the CURB65¹ have outperformed these guidelines. Modified systemic inflammatory response syndrome (SIRS) criteria outperform the original criteria in the perioperative period, presumably due to the influence of inflammatory processes in obscuring an infectious process.² Nevertheless, we will continue to use these over 20-year-old criteria as our guideline for defining disease states for this chapter (Table 10.1).

BACTEREMIA, SEPSIS, SEPTIC SHOCK, AND TSS

Bacteremia refers to the presence of viable bacteria in blood.³ To gain access to the circulation, bacteria and their toxins must penetrate through protective mechanisms such as anatomic barriers (skin), the nonspecific immune system, and the specific immune system. Bacteremia can range from a benign asymptomatic course to a more continual infection that can progress to septic shock. Bacteremia can be described as primary (direct invasion of bloodstream, as in neutropenic patients) or secondary (infection at another site complicated by microorganisms invading the bloodstream, as in pneumonia, infectious gastroenteritis, or soft-tissue infections). It can present as

- Transient bacteremia—short periods (minutes to hours) of viable bacteria in blood usually with pathogens felt to be “normal flora.” Common during toothbrushing, routine dental work, bowel movements, and menstruation. It is usually cleared by the reticuloendothelial system although the presence of impaired clearance (e.g., joint effusions),

implantable prosthetic devices, and damaged heart valves may all predispose to the establishment of infection and, potentially, persistent bacteremia.

- Intermittent bacteremia—recurrent episodes of intravascular recovery of viable bacteria originating from extravascular abscesses, cellulitis, or infections such as septic arthritis, peritonitis, or an empyema.
- Continuous bacteremia—usually occurring when infection is intravascular, such as in infective endocarditis or infected intravascular catheter, severe osteomyelitis, or with visceral abscesses.

There is a continuous increase in the incidence of bacteremia-associated mortality worldwide, mainly attributed to the increased use of invasive devices and invasive procedures, increased use of aggressive drug therapy that results in immunodeficiency, an increased population of critically ill patients due to advancements in life support, and advances in the development of highly sensitive diagnostic tools.⁴ Bacteremia can be community acquired or nosocomial in inheritance. Table 10.2 displays the most common pathogens seen in patients with documented bacteremia.

In studies documenting bacteremia, *Escherichia coli* was the most frequently isolated pathogen among older patients with community-acquired bacteremia. In contrast, *Staphylococcus aureus* was the most frequently isolated pathogen among younger adults with community-acquired bacteremia. *S. aureus* was the most common pathogen causing nosocomial bacteremia, regardless of age.⁵ The most common source of bacteremia is the urinary tract, with suspected cases followed by pneumonia and central venous catheter (femoral > subclavian) and wound infection.⁶ Many factors determine whether bacteremia will progress to sepsis, septic shock, or TSS. Elderly patients have an increased tendency to develop severe sepsis due to bacteremia compared to younger patients.^{5,7} Some other factors that can promote the progression to sepsis or septic shock are the immunocompetence of the patient, the virulence and number of pathogens in the blood, and the timing and nature of a therapeutic intervention.

Sepsis

Sepsis is a whole-body inflammatory response to an infection that may be life-threatening and is characterized as a systemic response manifested by two of the following, with evidence of infection³:

- Temperature >38°C or <36°C
- Heart rate >90 beats per minute
- White blood cell count >12,000 mcL, <4000 mcL or >10% immature (band) forms

Table 10.1 Definitions from 1992 Consensus Conference

Term	Definition
Infection	Inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms
Bacteremia	Presence of viable bacteria in blood
SIRS	Systemic inflammatory response to a variety of severe clinical insults manifested by two or more of the following conditions: (1) Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; (2) heart rate >90 bpm; (3) respiratory rate >20 breaths per minute or $\text{Pa}_{\text{CO}_2} <32$ mm Hg; or (4) white blood cell count $>12,000/\text{cu mm}$, $<4000/\text{cu mm}$, or $>10\%$ immature (band) forms
Sepsis	SIRS and documented or suspected infection
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities

Source: Adapted from Bone RC et al. *Chest* 1992;101:1644–1655.

Note: SIRS, systemic inflammatory response syndrome.

Table 10.2 Community-Acquired and Hospital-Acquired Bacteremia

	Gram-negative pathogens	Normal flora of
Community-acquired bacteremia and hospital-acquired bacteremia	<i>E. coli</i>	Small and large intestine
	<i>K. pneumoniae</i>	Large intestine
	<i>P. aeruginosa</i>	Small and large intestine
	Gram-positive pathogens	
	<i>S. aureus</i>	Anterior nares, skin, eye, upper respiratory tract, large intestine
	<i>S. pneumoniae</i>	Upper respiratory tract, eye, oral cavity
	<i>E. faecalis</i>	Small intestine

Due to the potential for rapid progression to severe sepsis or septic shock, sepsis is considered a true medical emergency, and thus rapid diagnosis is crucial to decrease morbidity and mortality. Sepsis is the leading cause of death in critically ill patients and among the top 10 overall causes of death in patients in the United States.⁸ Sepsis develops in 750,000 people annually, with 435,000 cases progressing to septic shock and more than 215,000 cases leading to death.^{9,10} There is a higher incidence in men than in women and in nonwhite persons than in white persons.¹¹ Although the median age of patients with a sepsis-related hospital discharge diagnosis is approximately 60 years, the incidence is high among infants (>500 cases/100,000 population per year), with low birth weight newborns experiencing particularly high risk.¹² Sepsis incidence and sepsis-related mortality decrease after the first year of life and then increase steadily with increasing age.⁹ Approximately 80% of cases of sepsis progressing to severe sepsis in adults occurred in individuals who were already hospitalized for another reason.^{13,14}

Sepsis is a clinical syndrome that can be caused by a variety of microorganisms (i.e., virus, bacteria, fungus, or parasites), although typically gram-negative and gram-positive bacteria account for most cases. In 30%–50% of septic cases, a definite microbial etiology was not found.^{14–16} Sepsis is defined as an immune response to microorganisms, and the number of organisms necessary to launch such a response varies depending on the patient's immune response to bacterial antigens.

Septic Shock

Septic shock is the clinical extension of sepsis with the addition of hypotension and secondary hypoperfusion of tissue

refractory to fluid administration, thus substantially increasing the mortality rate.³ Sepsis is usually reversible, whereas patients with septic shock often succumb despite aggressive therapy. Septic shock represents the most severe host response to infection. These patients do not display normal hemodynamic response to administered fluid bolus, and thus have persistent perfusion abnormalities, including tissue and organ hypoperfusion manifesting as lactic acidosis, oliguria, and/or acute alteration in mental status.¹⁷ These findings should yield high suspicion for multiple organ dysfunction syndrome (MODS), the most worrisome consequence of septic shock and most likely to result in mortality if not recognized and corrected early. Septic shock is the major cause of death in intensive care units; the mortality rate is as high as 50%–80% depending on the patient population.⁹ Septic shock and MODS are the most common causes of death in patients with sepsis.¹³ The incidence has increased owing to an increased number of patients who are immunocompromised, the increased use of invasive devices, and the growing elderly population.

Septic shock is part of the continuum associated with the systemic inflammatory response syndrome (SIRS). Although any microorganism may cause septic shock, it is most often associated with gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas*, and *Serratia*. Gram-positive bacteria such as *S. aureus* can also cause septic shock. Lower respiratory infections, abdominal infections, urinary tract infections, and soft-tissue infections are the nidus in, respectively, 35%, 21%, 13%, and 7% of documented cases of septic shock.^{18,19} Common factors or conditions that are associated with septic shock include diabetes mellitus, malnutrition, alcohol abuse, cirrhosis, respiratory infections, hemorrhage, cancer, and surgery.²⁰

Toxic Shock Syndrome

TSS is a rare, often life-threatening illness that develops suddenly after an infection and can rapidly progress, affecting many organ systems and requiring prompt recognition and medical treatment. It was first described in 1978 in seven children with *S. aureus* infections.²¹ After an epidemic in 1981, TSS has been typically associated with tampon use in healthy menstruating women. Due to physician and public awareness, the incidence of TSS has since declined in this population group, with the majority of documented cases now reporting men, neonates, and nonmenstruating women with TSS.²² A similar but more threatening TSS-like syndrome, streptococcal TSS, has emerged. It is associated with invasive and noninvasive streptococcal infections and has a rapidly progressive course and a high case-fatality rate. TSS is the result of infection by *Streptococcus pyogenes* or *S. aureus* bacteria.^{23,24} These pathogenic bacteria typically comprise a small percentage of the host's normal flora and usually do not cause severe disease. TSS occurs when these bacteria have an optimal environment for replication and toxin production that can enter the bloodstream and cause a severe immune reaction in immunosuppressed and/or immunocompetent persons. The host's immune response to bacterial toxins causes the symptoms associated with TSS.

Staphylococcal TSS came to prominence in 1980–1981, when numerous cases were associated with the introduction of superabsorbent tampons for use during menstruation.^{22,25} The disease is characterized by a fulminant onset, often in previously healthy persons. The diagnosis is based on clinical findings that include high fever ($>38.9^{\circ}\text{C}$), headache, vomiting, diarrhea, myalgias, and an erythematous eruption characterized as a sunburn. TSS usually develops from a site of colonization rather than infection.^{26–28}

Streptococcal TSS carries a mortality rate of 30% or higher, despite aggressive and timely medical therapy. Streptococcal TSS is epidemiologically distinct from other invasive infections in that younger and healthier populations are commonly affected.^{23,29} Group A β -hemolytic streptococcal (GAS) TSS may often originate in the skin of young, healthy patients at a site of local trauma. In 5%–10% of cases, there may be accompanying necrotizing fasciitis. Bacteremia has been shown to be a key component in a large majority of severe GAS infections.³⁰ TSS can occur as a consequence of GAS sinusitis, cellulitis, peritonitis, and tracheitis and as a complication of varicella infections.^{31,32}

TSS is separated into two distinct categories: menstrual and nonmenstrual. Both menstrual and nonmenstrual TSS have a higher incidence in white women. Although most cases of TSS are related to menstruation, nonmenstrual cases have increased and account for approximately one third of all cases. These nonmenstrual cases have been associated with localized or systemic infections, surgery, or insect bites. Patients with nonmenstrual TSS have a higher mortality rate than do those with menstrual TSS.²⁸

PATHOPHYSIOLOGY

Sepsis is the endpoint of a multifaceted process that begins with an infection. The initial host response is to mobilize inflammatory cells, neutrophils and macrophages, to the site of infection. These inflammatory cells then release circulating molecules that trigger a cascade of other inflammatory mediators that

result in a coordinated host response. If these mediators are not appropriately regulated, sepsis will occur. In the setting of ongoing toxin release, a persistent inflammatory response occurs with ongoing mediator activation, cellular hypoxia, tissue injury, shock, multiorgan failure, and (potentially) death. Much of the damage inflicted on the septic host is attributable to microbial toxins and the host's response to them.^{33–35}

In sepsis and septic shock, microbial antigens contain pathogen-associated molecular patterns that bind to the host protein's pattern recognition receptors, called toll-like receptors (TLRs), directing the activation of antibody-mediated immunity. Mutations associated with TLRs have been implicated in hyporesponsive antibody-mediated immunity, thus increasing certain patients' susceptibility to developing septic shock from gram-negative bacteria.^{36,37} One important microbial toxin in the pathogenesis of sepsis is lipopolysaccharide (LPS). LPS is the major structural component of the outer membrane of gram-negative bacteria. It is essential for cell viability for virtually all gram-negative bacterial pathogens.³⁸ LPS has no intrinsic toxic properties by itself.³⁹ The toxicity of LPS is related to the host response to this antigen (such an antigen is also termed a "superantigen"). Similar pathogen-associated molecular pattern mediators (superantigens) exist in gram-positive bacteria, lipoteichoic acid that induces a potentially harmful host response during sepsis.

LPS binds to LPS-binding protein, creating an LPS-LPS binding protein complex. This complex binds to the receptor located on the CD14 molecule that is found on monocytes, macrophages, and neutrophils. Peptidoglycans of gram-positive bacteria and LPS of gram-negative bacteria bind to TLR-2 and TLR-4, respectively. Given their central role in the recognition of microbes, TLRs are likely to have a crucial role in sepsis: TLRs are on the one hand essential for the early detection of pathogens, but on the other hand cause excessive inflammation after uncontrolled stimulation. TLR-2 and TLR-4 binding activates intracellular signal transduction pathways, which increase transcription of cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and interleukin-10 (IL-10).^{40,41} TNF- α , IL-1 β , and IL-6 are proinflammatory cytokines that activate an immune response but also cause both direct and indirect host cellular injury such as endothelial damage and eventually capillary leakage. LPS and TNF- α probably promote intravascular coagulation initially by inducing blood monocytes to express tissue factor, by initiating the release of plasminogen activator inhibitor type 1, and by inhibiting the expression of thrombomodulin and plasminogen activator by vascular endothelial cells. IL-10 is an antiinflammatory cytokine that inactivates macrophages, as well as alters monocyte function, decreases antigen-presenting activity, and reduces production of proinflammatory cytokines, and is underexpressed in the Th2-mediated immune response.^{36,41,42}

In TSS, the staphylococcal and streptococcal toxins are able to function as superantigens, which are proteins that simultaneously bind nonspecifically to T-cell receptors (TCRs) and major histocompatibility complex (MHC) class II molecules.⁴³ Toxic shock syndrome toxin 1 (TSST1), the best characterized of the toxins, binds to the MHC class II molecule.⁴⁴ These toxins are known as superantigenic, because they activate CD4 T-cell populations at a level that is at least five orders of magnitude greater than conventional antigens.⁴⁵ Superantigens are not processed by antigen-presenting cells. They bind directly to

MHC class II molecules expressed on antigen-presenting cells and cross-link with a large number of T cells that bear common V β chains and their TCRs. High concentrations of lymphokines and monokines result and induce TSS. Immune activation induced by superantigens potentiates the host response to other microbial mediators, including bacterial endotoxin.⁴⁶ The large numbers of effector CD4⁺ T cells resulting from this non-specific proliferation begin stimulating monocytes to secrete several cytokines, including TNF- α and IL-1. The secretion of these cytokines (instead of the localized secretion that normally occurs during infection) is the major determinant for morbidity associated with staphylococcal and streptococcal TSS.

CLINICAL AND LABORATORY AIDS REQUIRED FOR DIAGNOSIS

To diagnose bacteremia, sepsis, septic shock, or TSS as early as possible, it is necessary to recognize historic, clinical, and laboratory findings that are indicative of infection and organ dysfunction.¹⁸ A thorough physical examination is vital for the identification of the source of infection. Patients with bacteremia and often sepsis present a diagnostic challenge to clinicians owing to nonspecific, and sometimes nonexistent early clinical manifestations. The diagnosis must rely on a strong clinical suspicion supported by the presence of several of the signs of sepsis if possible. Two populations in which a high index of suspicion for bacteremia and sepsis should remain despite lack of clinical features are infants/children and the elderly population.^{6,47,48} Criteria for establishing diagnosis are within the definitions of bacteremia, sepsis, and septic shock, and thus one must consider the diagnosis, if a patient meets the criteria set forth from the 1992 consensus.³

BACTEREMIA, SEPSIS, AND SEPTIC SHOCK

Symptoms and signs that suggest the onset of sepsis are often nonspecific and include sweats, chills or rigors, breathlessness, nausea and vomiting or diarrhea, and headache.⁴⁹ Fever, often accompanied by shaking chills, is the most common clinical manifestation of bacteremia and sepsis. In a study of these findings, fever (temperature $>37.6^{\circ}\text{C}$) was seen in 82% of patients.^{50,51} Hypothermia (temperature $<36.4^{\circ}\text{C}$) was seen in 13% of bacteremic patients. Although the most common sign of bacteremic and septic patients is fever, a significant percentage of patients who present with bacteremia are also found to be hypothermic. Age, renal insufficiency, corticosteroid or antipyretic administration, and malignancy all increase the likelihood that a patient will not mount a febrile response. Mental status changes may occur in patients with bacteremia or sepsis. Changes may range from mild anxiety or restlessness to profound confusion. Change in mental state is an important clinical finding in elderly patients, who may exhibit few other early signs of disease. Tachypnea and altered mental status were more common among patients older than 75 years than among younger patients, whereas tachycardia⁵² and hypoxemia were less common among older patients. The hemodynamic instability of the young population with sepsis is of clinical importance. This effect is due to younger patients' ability to regulate blood pressure via vasoconstriction, leading to rapid onset of hypotension in this population.⁵³

A number of dermatologic manifestations have been described in patients with bacteremia, sepsis, septic shock,

and/or TSS. Skin may be the primary site of disease manifestation. To diagnose bacteremia, sepsis, or septic shock from cutaneous lesions, one must look at the overall picture in addition to the definition of the infection established in the 1992 consensus. Cutaneous lesions that occur as a result of bacterial infection can be divided into three categories:

1. Direct bacterial involvement of the skin and underlying soft tissues (e.g., cellulitis, erysipelas, and fasciitis)
2. Lesions that occur as a consequence of sepsis, hypotension, and disseminated intravascular coagulation (DIC; e.g., acrocyanosis and necrosis of peripheral tissues)
3. Lesions secondary to intravascular infections (e.g., microemboli and/or immune complex vasculitis)

Recognition of certain characteristic lesions can greatly assist etiologic diagnosis. There are three patterns of tissue involvement by gram-negative microbial pathogens⁵⁴:

1. Cellulitis and thrombophlebitis are associated with intense local inflammation. Bacteria implicated in case reports include *Campylobacter fetus*, *Vibrio* species, and *Aeromonas hydrophila*. Only a few bacteria are present in the affected tissues, however, making definitive diagnosis by Gram stain difficult as most biopsied lesions will contain very few organisms. For this reason, much better results may be obtained from culturing.
2. When the inflammatory response is impaired, usually by neutropenia, ecthyma gangrenosum or bullous lesions may occur; *Pseudomonas aeruginosa* is the most commonly isolated microorganism.
3. In symmetric peripheral gangrene associated with DIC, fibrin thrombi are seen in small vessels, but neither inflammatory cells nor bacteria are found.

Although often considered pathognomonic for *P. aeruginosa* bacteremia, ecthyma gangrenosum also has been observed in patients whose blood cultures grew *Klebsiella*, *Serratia*, *A. hydrophila*, or *E. coli*. Almost all patients with ecthyma gangrenosum are neutropenic at the time the lesions develop and are associated with lesions of skin or mucous membranes that rapidly worsen and evolve into nodular patches marked by hemorrhage, ulceration, and necrosis.^{54–57}

Ischemic changes (dusky or pallid color, coldness, loss of pulses) usually occur in the hands and feet, where they may follow thrombosis of small to medium-size arteries. Such ischemic changes are usually seen in septic shock. Inflammation-induced coagulopathy and vasoconstriction both contribute to their pathogenesis (Table 10.3).^{64,65}

Table 10.4 displays other common clinical signs and symptoms of sepsis and septic shock.

Laboratory Findings

Table 10.5 displays common laboratory findings seen in sepsis and septic shock.

TOXIC SHOCK

History and physical examination are vital in the identification of a presumptive source of TSS. Whereas septic shock

Table 10.3 Tissue Involvement by Gram-Negative Microbial Pathogens

Name	Suggestive of:	Description	Histologic findings
Palpable purpura ^{58–60}	<i>N. meningitidis</i> ; <i>H. influenzae</i> ; <i>R. rickettsii</i> ; <i>S. aureus</i>	> 3 mm, elevated, nonblanching, erythematous to violaceous plaques or nodules; dependent areas such as legs and feet are common areas; appears 12–36 h after onset of illness	Angiocentric inflammation with endothelial cell swelling fibrinoid necrosis and a neutrophilic cellular infiltrate around and within blood vessel walls Deposits of immunoglobulins and complement in blood vessel walls
Petechiae ^{58,61–63}	Infective endocarditis 2° to bacteremia; <i>N. meningitidis</i> ; <i>E. coli</i> ; other gram-negative bacteria	<3 cm, range from erythematous to violaceous; commonly found on lower legs but can also be found on the conjunctiva and palate; appears 12–36 h after onset of illness	Vascular thrombosis; perivascular hemorrhage
Ecthyma gangrenosum ^{54–57}	<i>P. aeruginosa</i> ; <i>A. hydrophila</i> ; gram-negative bacteria; <i>V. vulnificus</i>	Painless, round, erythematous macules; they become indurated and progress to hemorrhagic bluish bullae; lesions later slough to form a deep gangrenous ulcer with a gray-black eschar and a surrounding erythematous halo; process evolves rapidly over a period of 12–24 h; usually found between umbilicus and knees but may occur anywhere on the body	Bacterial invasion of the media and adventitia of vein walls deep in the dermis Sparing of the intima and lumen Minimal inflammation
Acrocyanosis ^{64,65}	Septic shock DIC	Blueness of hands and feet with preserved pinkness in mucous membranes	
Hemorrhagic bullous ^{66,67}	<i>V. vulnificus</i> (contact with seafood)	Erythematous painful swollen limb (lower > upper) with bilateral hemorrhagic plaques and bullae; develops 36 h after onset	Noninflammatory bulla, epidermal necrosis, hemorrhage, and bacteria in dermal vessels
Cellulitis ^{68,69}	<i>S. aureus</i> <i>S. pyogenes</i> <i>S. pneumoniae</i> Gram-negative bacilli	Not raised, and demarcation from uninvolved skin is indistinct; tissue feels hard on palpation and is extremely painful; cellulitis extends into subcutaneous tissues	

Note: DIC, disseminated intravascular coagulation.

Table 10.4 Clinical Signs and Symptoms of Sepsis and Septic Shock

System	Clinical symptoms
CNS ^{69,70}	Confusion Focal signs, seizures, and cranial nerve palsies are rare Encephalopathy (may be associated with a poor prognosis) Diffuse weakness
Endocrine	Hypotension Hypoglycemia or hyperglycemia Adrenal insufficiency
Cardiovascular	Tachycardia
Pulmonary	Hyperventilation
Renal	Oliguria
GI	Nausea/vomiting/diarrhea Ileus Upper GI bleeding from stress ulcers
Hepatic	Jaundice

Note: CNS, central nervous system; GI, gastrointestinal.

has hypotension and subsequent organ failure, toxic shock is characterized as coinciding hypotension with organ failure. TSS caused by *S. aureus* and TSS caused by *S. pyogenes* are both characterized by an acute illness with fever, sudden-onset hypotension, rapidly accelerated renal failure, and multisystem

organ failure. Clinical definitions of staphylococcal and streptococcal TSS are described in Tables 10.6 and 10.7, respectively. Both types of syndrome also have differences that can help differentiate them on clinical appearance. Table 10.8 highlights those differences. The presence of fever, vomiting, watery

Table 10.5 Laboratory Findings in Sepsis and Septic Shock

Laboratory study	Findings	Comments
White blood cell count	Leukocytosis or leucopenia	Stress response, increased margination of neutrophils in sepsis; toxic granulation may be seen; occasionally, bacteria may be found in the peripheral blood smear
Platelet	Thrombocytopenia	Look for evidence of fragmentation hemolysis in the peripheral blood smear; thrombocytopenia may or may not be accompanied by disseminated intravascular coagulation
Glucose	Hyperglycemia or hypoglycemia	Acute stress response, inhibition of gluconeogenesis
Clotting factors	Prolonged prothrombin time, activated partial thromboplastin time, low fibrinogen levels, and evidence of fibrinolysis	Coagulopathy often seen with systemic endotoxin release
Liver enzymes	Elevated alkaline phosphatase, bilirubin, and transaminases; low albumin	—
Blood cultures	Bacteremia or fungemia	The presence of positive blood culture does not make the diagnosis, and its absence does not exclude the diagnosis
Plasma lactate	Mild elevations (>2.2 mmol/L)	Hypermetabolism, anaerobic metabolism, inhibition of pyruvate dehydrogenase
C-reactive protein	Elevated	Acute-phase reactant, sensitive but not specific for sepsis
Arterial blood gas	Respiratory alkalosis (early); metabolic acidosis (late)	Measurements of O ₂ content and mixed venous O ₂ saturation useful in management
Serum phosphate	Hypophosphatemia	Inversely correlated with high levels of inflammatory cytokines

Table 10.6 Major Criteria for Diagnosis of *S. Aureus* TSS

1. **Fever:** Temperature $\geq 38.9^{\circ}\text{C}$ (102°F)
2. **Eruption:** Diffuse macular erythroderma ("sunburn" eruption)
3. **Hypotension:** Systolic blood pressure (BP) ≤ 90 mm Hg (adults) or less than fifth percentile for age (children <16 years old); or orthostatic hypotension (orthostatic drop in diastolic BP by 15 mm Hg, orthostatic dizziness, or orthostatic syncope)
4. **Involvement of at least three of the following organ systems:**
 - a. Gastrointestinal (vomiting or diarrhea at onset of illness)
 - b. Muscular (severe myalgias or serum creatine phosphokinase level at least twice the upper limit of normal)
 - c. Mucous membranes (vaginal, oropharyngeal, conjunctival hyperemia)
 - d. Renal (blood urea nitrogen or creatinine level at least twice upper limit of normal or pyuria)
 - e. Hepatic
 - f. Hematologic (thrombocytopenia)
 - g. Central nervous system
5. **Desquamation:** 1–2 weeks after onset of illness (typically palms/fingers, soles/toes)
6. **Evidence against alternative diagnosis:** Negative results of cultures of blood, throat, or cerebrospinal fluid (if performed); no increase in titers of antibody to the agents of Rocky Mountain spotted fever, leptospirosis, and rubeola (if obtained)

Probable diagnosis:

- Desquamation and three other major criteria
- All five major criteria in the absence of desquamation

Note: TSS, toxic shock syndrome.

Table 10.7 Major Criteria for Diagnosis of *S. Pyogenes* TSS

1. **Isolation of group A β -hemolytic streptococci**
From a normally sterile site (e.g., blood, cerebrospinal fluid, peritoneal fluid, tissue biopsy specimen)
From a nonsterile site (e.g., throat, sputum, vagina)
2. **Hypotension:** systolic blood pressure <90 mm Hg in adults or lower than the fifth percentile for age in children
3. **Two or more of the following signs:**
 - Renal impairment: creatinine level >177 $\mu\text{mol/L}$ (≥ 2 mg/dL) for adults or two times or more the upper limit of normal for age
 - Coagulopathy: platelet count $\leq 100,000/\text{mCL}$ or disseminated intravascular coagulation
 - Hepatic involvement: ALT, AST, or total bilirubin levels two times or more the upper limit of normal for age
 - Adult respiratory distress syndrome
 - Generalized erythematous macular eruption that may desquamate
 - Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

An illness fulfilling criteria 1(a), 2, and 3 can be defined as a definite case. An illness fulfilling criteria 1(b), 2, and 3 can be defined as a probable case if no other cause for the illness is identified.

Notes: TSS, toxic shock syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 10.8 Differences in Staphylococcal and Streptococcal TSS

Characteristics	Staphylococcal TSS	Streptococcal TSS
Predisposing factors	Tampons, burns, wounds	Varicella, wounds
Site of infection	Superficial (i.e., impetigo, burns, diaper rash, genital tract)	Deep (i.e., blunt trauma, necrotizing fasciitis, myositis, septic joint)
Abrupt onset of pain	Rare	Common
Eruption	Very common	Less common
Vomiting/diarrhea	Very common	Less common
Increased creatinine kinase	Rare	Common in fasciitis
Bacteremia	<5%	60%
Desquamation	7–14 days	Less common
Mortality	3%–5%	5%–10%

Note: TSS, toxic shock syndrome.

diarrhea, myalgias, and conjunctival hyperemia are suggestive of *S. aureus* TSS, whereas soft-tissue infections such as cellulitis, abscess, or necrotizing fasciitis with increased pain commonly occur with streptococcal TSS. Both can form without an identifiable source of infection.

Staphylococcal TSS

Staphylococcal TSS should be suspected in any individual with a sudden onset of a fever ($>38.9^{\circ}\text{C}$) with chills, malaise, vomiting or diarrhea, myalgias, dizziness, syncope, beefy edematous mucous membranes, and/or conjunctival hyperemia.

In addition to signs and symptoms, there may be a history of superabsorbent tampon use, recent surgery, diaphragm contraception, or indwelling foreign body. On physical examination, the patient appears ill and has a fever $>38.9^{\circ}\text{C}$. There may be clinical evidence of hypotension, peripheral edema, and muscle tenderness. If an infected wound is the source of TSS, the clinical presentation will be out of proportion to the wound presentation. Skin examination shows that there is a flexurally accentuated diffuse nonpruritic, blanching macular-papular erythroderma, described as “sunburn.” The distribution always involves the extremities, with erythematous palms and soles. Erythema of the mucous membranes is commonly observed as well. The eruption may be subtle and is often missed in heavily pigmented patients or when the patient is examined in a poorly illuminated room. The eruption fades in approximately 3 days, but sheet-like desquamation of the hands and feet occurs in all patients 5–12 days after the eruption disappears. Some patients also may develop reversible alopecia and nail shedding. In menstrual TSS, edema and erythema of the inner thigh and perineum with a normal uterine and adnexal examination may be noted. In nonmenstrual TSS, another focus of infection may be present.

Laboratory findings reflect dysfunction of several organ systems. Laboratory abnormalities included as criteria for diagnosing TSS are elevated creatinine phosphokinase, acute renal insufficiency, sterile pyuria, elevated liver function tests, and thrombocytopenia. Some laboratory findings that are not included in the criteria for TSS but can commonly be seen are electrolyte abnormalities (hypophosphatemia and hypocalcemia), leukocytosis, and decreased serum albumin and total protein due to capillary leakage. The prothrombin, international normalized ratio, and partial thromboplastin times may be elevated, with or without thrombocytopenia. Laboratory abnormalities usually return to normal within 7–10 days of disease onset. Cultures of material from the vagina or cervix

are usually positive for *S. aureus*. Blood cultures are negative in 85% of patients with TSS but must still be obtained.

Streptococcal TSS occurs in all age groups without a predisposing factor. A hallmark feature of *S. pyogenes* TSS is pain that is severe and abrupt in onset. The pain is usually preceded by tenderness. Symptoms and signs that remain the hallmark in staphylococcal TSS (such as fever, chills, myalgias, vomiting, and diarrhea) are present in less than 20% of streptococcal cases. Most cases present with fever and a localized soft-tissue infection that can progress to necrotizing fasciitis or myositis and require surgical debridement or even amputation. Laboratory data on streptococcal TSS cases are similar to those on staphylococcal TSS. Symptoms of streptococcal TSS are non-specific. Physicians should have clinical suspicion in children and in persons with chronic underlying illness. Clues to suggest streptococcal TSS are localized severe pain as opposed to myalgia, skin lesion, or history of trauma at the site of pain.

THERAPY

Successful management of bacteremia requires elimination of the offending pathogen by the timely administration of antimicrobials and removal of the source of infection. Bacteremia should be treated, if one obtains two to four positive blood cultures; sensitivity is dependent on the volume of blood cultured, with 30–40 mL per session being recommended for optimal results. One must draw at least 10 mL of blood for culture by venipuncture with at least 10 mL through each lumen of a central vascular catheter when one is present. Empiric antimicrobial therapy of bacteremia and sepsis depends on localizing the site of infection to a particular organ, which determines the pathogenic flora in the septic process. The usual pathogens are determined by the organ or infection site, are predictable, and are the basis for the selection of appropriate empiric antimicrobial therapy. Coverage should be directed against the most common pathogens and does not need to be excessively broad or contain unnecessary activity against uncommon pathogens. If multiple drugs are used initially, the regimen should be modified and coverage narrowed based on the results of culture and sensitivity testing.

When sepsis is identified, treatment should be started immediately. To aid in uniform and consistent management, two sets of severe sepsis bundles were defined by the 2002 Surviving Sepsis Campaign: the sepsis resuscitation bundle and the sepsis management bundle (Tables 10.9 and 10.10). The resuscitation bundle should be implemented within the

Table 10.9 Sepsis Bundles**Sepsis resuscitation bundle**

1. Serum lactate measured
2. Blood cultures obtained before antibiotics administered
3. Improve time to broad-spectrum antibiotics
4. In the event of hypotension or lactate >4 mmol/L (36 mg/dL):
 - a. Deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent)
 - b. Apply vasopressors for ongoing hypotension
5. In the event of persistent hypotension despite fluid resuscitation or lactate >4 mmol/L (36 mg/dL):
 - a. Achieve central venous pressure of 8–12 mm Hg
 - b. Achieve central venous oxygen saturation of $\geq 70\%$

Sepsis management bundle

1. Administer low-dose steroids
2. Administer drotrecogin alfa (activated)
3. Maintain adequate glycemic control
4. Prevent excessive inspiratory plateau pressures

Table 10.10 Suggested Initial Drug Therapy Based on Presumed Source

Source	Antibiotic treatment	Comment
Community-acquired pneumonia	Erythromycin ^a and third-generation cephalosporin ^b OR First- or second-generation cephalosporin ^c plus aminoglycoside ^d	Gram-negative bacteria cause 10%–20% of community-acquired pneumonias requiring hospitalization; <i>H. influenzae</i> , <i>K. pneumoniae</i> , and others implicated; consider <i>Legionella</i> species if patient is elderly or immunosuppressed
Hospital-acquired pneumonia	Antipseudomonal β -lactam ^e plus aminoglycoside ^d	Must treat for more resistant organisms including <i>P. aeruginosa</i>
Urinary tract infections	Ampicillin ^a plus aminoglycoside ^d	Combination also covers enterococci
Intraabdominal or biliary tract infections	β -Lactam inhibitor ^f plus aminoglycoside OR Imipenem plus aminoglycoside	Use against enteric gram-negative bacteria and anaerobes
Neutropenic patients	Antipseudomonal β -lactam ^e plus aminoglycoside ^d	Add vancomycin for <i>Staphylococcus</i> species if intravascular catheter is present
Unknown source	Imipenem or β -lactam inhibitor ^f plus aminoglycoside ^d	Add vancomycin if gram-positive infection is a consideration

Source: Data from Stein, J.H., editors. *Internal Medicine*, 5th ed. Mosby-Year Book, St. Louis, 1998.

^a Others: Ampicillin 1–2 g every 4–6 h; erythromycin 0.5–1 g every 6 h; ticarcillin clavulanate 3.1 g every 4–8 h; vancomycin 1 g every 12 h.

^b Cefotaxime 1–2 g every 6–8 h; ceftriaxone 1–2 g every 24 h; ceftazidime 1–2 g every 8 h.

^c Cefazolin 1 g every 8 h; cephalothin 1–2 g every 4–6 h; cefuroxime 1 g every 8 h.

^d Gentamicin, tobramycin 3–5 mg/kg/d divided every 8 h; amikacin 15 mg/kg/d divided every 8 h. Must adjust for renal dysfunction.

^e Piperacillin, mezlocillin, ticarcillin 3 g every 4 h; ceftazidime 1–2 g every 8 h; imipenem 500 mg every 6 h.

^f Ticarcillin clavulanate 3.1 g every 4–6 h; piperacillin/tazobactam 3 g every 4–6 h.

initial 6 hours after patient admission to the hospital. It is also recommended to implement the sepsis management bundle as soon as possible but within the first 24 hours.⁷²

For TSS, hemodynamic stabilization and antimicrobial therapy are the initial goals of treatment. Immediate and aggressive management of hypovolemic shock is critical. Fluid resuscitation with crystalloid or colloidal solution is important in the mainstay of treatment. Tampons or other packing material should be promptly removed. It is often difficult to determine initially whether *Streptococcus* or *Staphylococcus* is the offending bacterium, so coverage for both is necessary. Suggested regimens include penicillin plus clindamycin, erythromycin, or ceftriaxone plus clindamycin. Patients with suspected methicillin-resistant staphylococcal (MRSA) TSS should be treated with IV vancomycin 1 g every 12 hours for 10–15 days, with dose adjustment based on creatinine clearance; alternatively, additional anti-MRSA agents, such as linezolid, daptomycin, teicoplanin, ceftaroline or telavancin, may be considered.

Patients with streptococcal TSS require hospitalization for care, usually initially in an intensive care setting. Patients with streptococcal TSS should be treated with both IV penicillin G, 3–4 million units every 4 hours, and IV clindamycin, 600–900 mg every 8 hours for 10–15 days, followed by oral therapy. Studies in an experimental mouse model of streptococcal myositis have shown penicillin was not effective, when administered as early as 2 hours after infection, whereas clindamycin-treated mice, even when treated as long as 16 hours after infection, had a survival rate of 70%.^{73,74} An observational study has shown a lower 30 day mortality with clindamycin (15%) than in those who did not receive clindamycin (39%).⁷⁵

PROGNOSIS

Severe sepsis and septic shock are associated with case-fatality ratios of approximately 30% and 50%, respectively. Outcome is significantly (and most profoundly) influenced by the patient's

underlying disease. Bacteremia with certain microbes (e.g., *S. aureus*) may also be independently related to mortality in multivariate analyses. Of the many studied biologic markers, plasma IL-6 levels and a high IL-10/TNF- α ratio may correlate best with risk of dying. None of these measurements warrants routine use.

The mortality rate in patients with staphylococcal TSS is 5%–15%, whereas that for streptococcal toxic shock syndrome may be five times higher.

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Staphylococcal scalded skin syndrome

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Staphylococcal scalded skin syndrome (SSSS) is the term used to define a potentially life-threatening, blistering skin disease caused by exfoliative toxins (ETs) of certain strains of *Staphylococcus aureus*. The syndrome belongs to a wide spectrum of staphylococcal infections that range in severity from localized bullous impetigo to a generalized cutaneous involvement characterized by extensive blistering with superficial denudation and subsequent desquamation of the skin. SSSS is so-named due to its staphylococcal etiology and its remarkable resemblance to the clinical picture of scalding.

HISTORY

The original description of the syndrome dates back to 1878, when Gottfried Ritter von Rittershain (1820–1883), director of an orphanage in Prague, reported approximately 300 cases of *dermatitis exfoliativa neonatorum*. A relationship between the disease and staphylococci was perceived at the beginning of the twentieth century, but only in the early 1950s did the link between bullous impetigo and phage group 2 staphylococci become evident. Lyell's report on toxic epidermal necrolysis (TEN) in 1956 drew attention to the similarities between this drug-induced condition and the appearance of extensive scalding, but this also led to a period of confusion between nonbacterial (immune-mediated) TEN and bacterial (staphylococcal) toxin-mediated scalded skin syndrome.¹ In the early 1970s, the development of a murine model of the staphylococcal disease clarified the situation.² Nowadays, SSSS is clearly distinguished from other diseases of generalized epidermal necrolysis, and the term *Ritter disease* is still used to describe generalized SSSS in newborns.

EPIDEMIOLOGY

SSSS, which may be present in epidemic form as well as sporadically, is primarily a disease of infancy and early childhood with most cases occurring in children younger than 6 years. The median age of onset is 1 year 10 months. There has been one case report of congenital SSSS in a neonate with sepsis, born to a mother with staphylococcal chorioamnionitis.³ Occasionally, adults with chronic renal insufficiency or who are immunosuppressed can be affected. Because the toxins responsible for the lesions are excreted renally, infants, who have naturally immature kidneys, and adults with renal failure are obviously the most common candidates for this disease.

In addition to decreased toxin clearance, lack of immunity to the toxins may play a role. Outbreaks of SSSS have often occurred in neonatal nurseries as a consequence of asymptomatic carriage of a toxigenic strain of *S. aureus* by health-care workers or parents. In fact, standard infection control

measures, such as the use of chlorhexidine hand washing, may not be always sufficient for prevention, because the presence of potentially pathogenic staphylococci in the nasal cavities of a healthy adult carrier can be a point source for infection.

A slight male-to-female predominance of SSSS has been documented (1.25:1).⁴

ETIOLOGY

The cause of SSSS is related to bacteria belonging to the genus *Staphylococcus*. This genus encompasses spherical gram-positive bacteria, irregularly grouped in cluster-like formations. They are immobile and asporogenic microorganisms, and, from a metabolic perspective, are facultative aerobes-anaerobes. This genus includes bacteria that are pathogens for both humans and other mammals. Traditionally, staphylococci are subdivided into two groups according to their ability to coagulate plasma. *S. aureus*, which is pathogenic for humans, belongs to the coagulase-positive group; the coagulase-negative group includes 32 species that have been isolated in humans. The latter constitute the normal flora of the skin and mucosa, although some of them can cause infections in neonates, elderly persons, and immunodepressed subjects. *S. aureus* owes its name to the carotenoid pigment produced during multiplication that gives its colonies a yellow-orange color. To isolate *S. aureus* in samples contaminated by a mixed flora, a selective medium containing 7% NaCl is needed as this inhibits the multiplication of most microorganisms but not of *S. aureus*. If mannitol (Chapman medium) is added to the NaCl medium, the sugar is fermented by *S. aureus* but not by the other staphylococci, thus allowing differentiation of the species. *S. aureus* is a ubiquitous microorganism that permanently colonizes the epidermis around the nostrils in 20% of the population, is usually associated with transient flora, and can occasionally cause infections. *S. aureus* infections underlie several clinical patterns that differ considerably according to the site of infection and the means of transmission (direct extension or metastatic or hematogenous diffusion). *S. aureus*, in particular, is the most frequent etiological agent in common skin infections, such as folliculitis, furuncle, and carbuncle that arise in the sebaceous glands and hair follicles where the microorganism produces lipolytic enzymes that allow both the degradation of the sebum (and as a result of the lipid components with antibacterial activity) and the use of the lipids themselves as a source of metabolic energy. The pathogenic action of *S. aureus* depends both on a series of factors that favor multiplication in vivo and on the production of numerous toxins and isoenzymes.

The strains of *S. aureus* responsible for the onset of SSSS are producers of epidermolytic or exfoliative toxin (ET) and are often penicillin resistant.⁵ Although most toxigenic strains of *S. aureus* are identified by group 2 phage (types 71 and 55), toxin

producers have also been identified among phage groups 1 and 3.² The frequency of isolation of strains of toxin-producing *S. aureus* varies from place to place, but is generally less than 10%. ET is produced by the microorganism in two antigenically distinct forms, both capable of causing the disease (ET-A and ET-B). ET-A, a thermostable protein, is encoded by a chromosomally located gene; ET-B, which is encoded by a gene located in the plasmids, is a thermolabile protein.^{6,7}

PATHOGENESIS

More than 30 years ago it was shown that the blisters in SSSS are caused by an ET released by virulent strains of *S. aureus* dwelling in distant foci of infection, such as the pharynx, nose, ear, or conjunctiva. It was surmized that ET, produced by staphylococci, and released into circulation, reached the skin and caused blistering and shedding of the epidermis at sites that were distant from the infection. In fact, the formation of superficial epidermal blisters and extensive skin exfoliation, similar to those observed in patients with SSSS, were experimentally obtained in neonatal mice into which purified staphylococcal ET was injected. The presence of ET in the blood induced the production of protective neutralizing antibodies and, as a consequence, lasting immunity, which could account for the fact that adolescents and adults are rarely affected by SSSS. Subsequently, it was discovered that two major serotypes of this toxin, ET-A and ET-B, are responsible for the pathogenic changes of the syndrome.⁸ ET-A is the predominant ET isoform in Europe and the United States, whereas ET-B is the most frequent isoform in Japan. ET-B-producing *S. aureus* is, however, the predominant strain isolated in generalized SSSS.

Exactly how exfoliative toxin causes these blisters was controversial for many years. Early studies reported that ETs were mitogenic in human and murine lymphocytes, suggesting that the toxins act as superantigens and stimulate certain V β T-lymphocyte clones nonspecifically via major histocompatibility complex class II molecules. Histopathologic observations of the cutaneous lesions in SSSS patients, however, have generated controversy regarding the superantigen theory of ETs, because the SSSS skin lesions fail to show evidence of intense T-cell recruitment into the epidermis, where the blisters occur. In addition, patients exhibit only a loss of cell-cell adhesion, but no induced keratinocyte necrosis as would be expected with superantigen-stimulated T cells. Because purified recombinant ET-A produced in a non-toxin-producing strain of *S. aureus* was unable to stimulate human and murine T cells, it was suggested that the superantigen activity of ETs was probably due to contamination by other mitogenic exotoxins.⁷

The potency of ETs as serine proteases has also been examined. Comparison of the deduced amino acid sequences of ET-A and ET-B (they comprise 242 and 246 amino acids, respectively, and share approximately 40% amino acid homology) showed that they share primary amino acid homology with staphylococcal V8 protease, which belongs to a family of trypsin-like serine proteases.

When ET-A and ET-B were cloned, they revealed amino acid sequences and crystal structures suggestive of serine proteases. In some crystal solution, this structure was slightly irregular in that one peptide bond in the catalytic site was rotated 180° in the wrong direction to form an active catalytic pocket. These findings indicated that exfoliative might not be active as a protease unless it bound a specific substrate that was able to reform its catalytic pocket.⁷

Both ET isoforms cleave human and mouse desmoglein 1 (dsg 1), a desmosomal intercellular adhesion molecule, at one position after glutamic acid residue 381, between extracellular domain (EC) 3 and EC 4. This cleavage site is located in the putative calcium-binding site of dsg 1, and the removal of the calcium ions blocks the cleavage of dsg 1 by both ET-A and ET-B. The importance of this site was demonstrated by the replacement of the catalytic serine-195 of ET-A with a cysteine or glycine residue, which resulted in a loss of exfoliating activity after injection into neonatal mice.⁶

These findings suggest that the serine protease activities of ET-A and ET-B are involved in intraepidermal blister formation in patients with SSSS.⁷ ET cleaves dsg 1 by the key-in-lock mechanism that is common to many proteolytic enzymes with limited substrate specificities. This remarkable mechanism efficiently targets one molecule, dsg 1, which allows *Staphylococcus* to grow below the epidermal barrier but superficially enough to be contagious through skin contact; however, neither the enzymatic activities of ETs nor their specific substrates were recognized at the time. To determine whether ET-A cleaves dsg 1 directly, the toxin was incubated in vitro with baculovirus recombinant ECs of human dsg 1, human dsg 3, mouse dsg 1-a (one of three mouse dsg 1 isoforms), and mouse dsg 3. ET-A was shown to cleave human and mouse dsg 1-a in a dose-dependent fashion, but not dsg 3. ET-B also was found to cleave the ECs of human and mouse dsg 1-a specifically and directly.⁹ A major breakthrough in understanding the mechanism of ET-mediated blistering came in 2000, when similarities were noted between SSSS and an autoimmune blistering skin disease, pemphigus foliaceus (PF).¹⁰ In PF patients, immunoglobulin G (IgG) autoantibodies disrupt the intercellular adhesion of keratinocytes and cause epidermal blistering. The target molecule for IgG autoantibodies in PF is dsg 1. The extracellular region of dsg contains five cadherin repeats separated by putative calcium-binding domains. In humans, four dsg isoforms (dsg 1, 2, 3, 4) with tissue- and differentiation-specific distribution patterns have been identified. In all desmosome-bearing tissues, dsg 2 is present, whereas dsg 1 and dsg 3 are found predominantly in stratified squamous epithelia. In humans, dsg 1 is expressed throughout the epidermis but most intensely in superficial layers. The expression of dsg 3 is restricted to the basal and immediate suprabasal layers, although in human oral mucous membranes, dsg 1 and dsg 3 are expressed throughout the epithelia, with dsg 1 expression being much lower than that of dsg 3. The expression of dsg 2 and dsg 4 in the human epidermis is restricted to the basal layer and just below the cornified layer, respectively. In PF, blisters are observed exclusively in the superficial epidermis, where dsg 1 is predominantly expressed with no coexpression of other dsg isoforms.⁷

Five important clues from PF studies indicated that the substrate of the ETs might be dsg 1 (Table 11.1). These clues

Table 11.1 Similarities between Pemphigus Foliaceus (PF) and Staphylococcal Scalded Skin Syndrome (SSSS)

Clinical features: scaly and crusted superficial erosions
Skin (not mucous membranes) are involved
Site of cleavage: just below the stratum corneum
The crucial point where cleavage occurs is a Ca ²⁺ binding domain in the extracellular region of desmoglein 1
Identical appearance of experimentally induced lesions in neonatal mice injected with either PF immunoglobulin G antibodies or staphylococcal exfoliative toxins

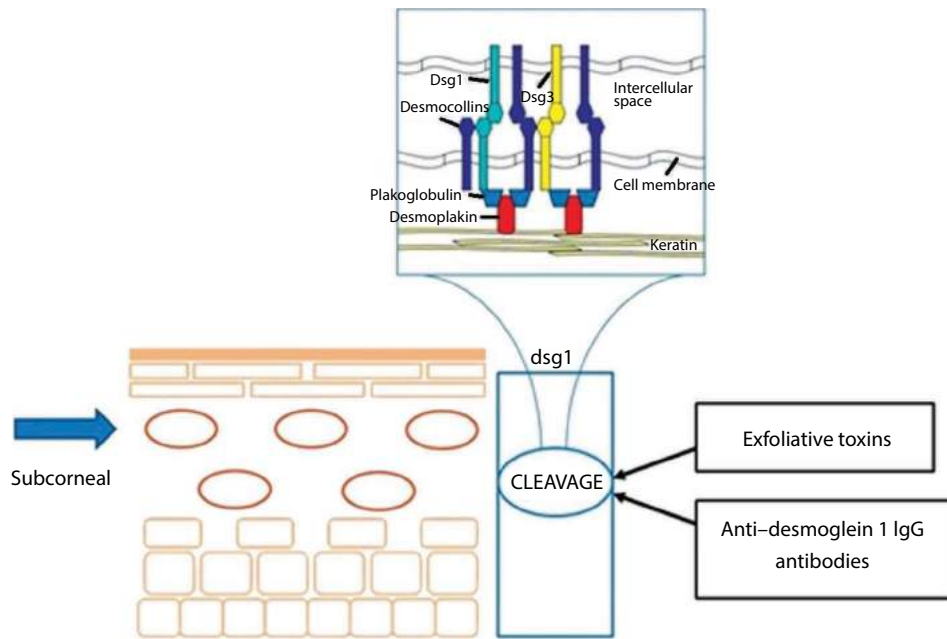


Figure 11.1 Identical cleavage site in staphylococcal scalded skin syndrome (SSSS) and pemphigus foliaceus (PF). (IgG, immunoglobulin G; dsg 1, desmoglein 1.)

suggested that the ETs, such as PF IgG, might target dsg 1. If dsg 1 were cleaved specifically by the ETs, then, just as in PF, “desmoglein compensation” would account for the localization of the blisters in SSSS in the upper portion of the epidermis and for the absence of the blisters in the mucous membrane. The dsg compensation theory rests on the following two observations: anti-dsg 1 or anti-dsg 3 autoantibodies inactivate only the corresponding dsg, and functional dsg 1 or dsg 3 alone is usually sufficient for cell-cell adhesion. Anti-dsg 1 IgG autoantibodies in serum from patients with PF cause superficial blisters in the skin; no blisters form in the lower portion of the epidermis or mucous membranes, because dsg 3 maintains cell-cell adhesion in those areas. In SSSS, the ETs produced by *S. aureus* act as dsg 1-specific molecular scissors and cleave dsg 1 but not dsg 3, resulting in superficial epidermal blisters only, because, in the upper layers of the epidermis, the cohesive function of the impaired dsg 1 cannot be compensated by other dsgs isoforms, as occurs elsewhere. Although pemphigus and SSSS are unrelated diseases, the identical histopathology of the superficial type of the IgG-mediated disorder (PF) and lesions in neonatal mice treated with staphylococcal ETs clearly indicates that staphylococcal ETs act on the same autoimmune target of PF (i.e., dsg 1), thus provoking identical specific cleavage within the superficial layer of the epidermis (Figure 11.1). Interestingly enough, about two centuries ago, astute clinicians realized that staphylococcal bullous diseases were clinically similar enough to pemphigus to name SSSS (along with its localized form, bullous impetigo) in infants “pemphigus neonatorum.”

CLINICAL FEATURES

The onset of SSSS may either be acute with fever and dermatitis or be preceded by a prodrome of malaise, irritability, and

cutaneous tenderness, often accompanied by purulent rhinorrhea, conjunctivitis, or otitis media. The typical eruption presents as a faint, orange-red, macular exanthem, localized initially on the head (Figure 11.2) and spreading within a few hours to the remainder of the body, with peculiar periorificial



Figure 11.2 Clinical features of SSSS. Erythema, edema, and crusting of face. (Courtesy of Rosalba Picciocchi and Orsola Ametrano, Naples, Italy.)



Figure 11.3 Clinical features of SSSS. Nikolsky sign evoked on left forearm after rubbing. (Courtesy of Rosalba Picciocchi and Orsola Ametrano, Naples, Italy.)

and flexural accentuation. Edema of the hands and feet may be observed. At this stage, cutaneous tenderness is a distinctive feature as proven by the easy disruption of skin after firm rubbing or pressure (Nikolsky sign) (Figure 11.3). Within 24–48 hours, the macular exanthem gradually turns into a blistering eruption; in particular, a characteristic tissue-paper-like wrinkling of the epidermis heralds the appearance of large, flaccid bullae. Blistering usually starts in the axillae and groin, as well as on periorificial areas. Subsequently, the entire body is affected. One or two days later, the bullae rupture, and their roofs are sloughed, leaving behind a moist, glistening, red surface along with varnish-like crusts. At this stage, the clinical appearance closely resembles that of extensive scalding (Figure 11.4). The patient becomes irritable, sick, and feverish, with “sad man” facies, perioral crusting, lip fissuring, and mild facial edema. Mucous membranes are usually spared by bullae and erosions, but generalized mucous membrane erythema, especially intense in the conjunctiva (under which there may be



Figure 11.4 Clinical features of SSSS. Diffuse erythema of back associated to large areas of “scalded skin.” (Courtesy of Rosalba Picciocchi and Orsola Ametrano, Naples, Italy.)

hemorrhage), is often observed. Days later, due to generalized shedding of the epidermis, scaling and desquamation progressively occur. The skin returns to normal in 2–3 weeks. Scarring is not usually a feature.

An abortive mild form of SSSS may be seen.⁸ The early erythrodermic picture evolves into a desquamative condition with the absence of a blistering stage. This clinical form is often associated with occult bone and joint infections or contaminated wounds.

PATHOLOGY

Under light microscopy SSSS is characterized by intraepidermal cleavage with clefts appearing in the granular layer or just beneath the stratum corneum and leading to the formation of bullous cavities (Figure 11.5). Few or no inflammatory cells are present within the blister. A few acantholytic cells are often seen either adjoining the cleavage plane or free-floating in the bulla. A scanty lymphocytic infiltrate may surround superficial blood vessels in the dermis. In fresh lesions, no bacterial organisms can be seen on Gram stain of the biopsy specimens, whereas older lesions can become superinfected thus obscuring an SSSS diagnosis.

DIAGNOSIS

The diagnosis of SSSS is mainly clinical and should be taken into consideration in any child who develops a generalized, tender erythema, most prominent on periorificial (in particular perinostril and periocular) areas, associated with Nikolsky sign. Suspected SSSS is supported by the confirmation of staphylococcal infection in different sites (conjunctiva, nasopharynx, ear). Cultures taken from intact bullae are negative, because

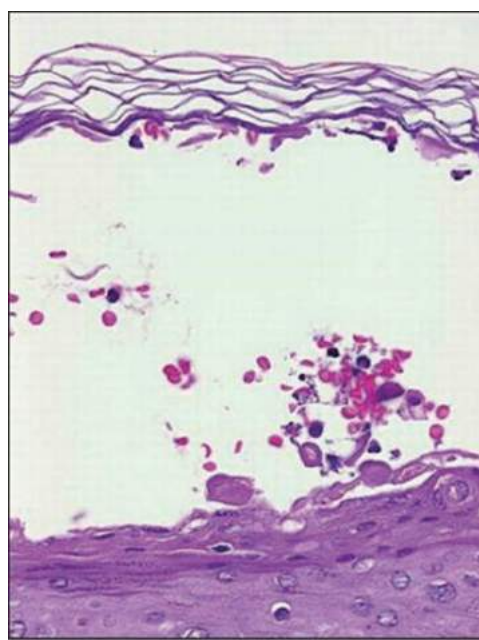


Figure 11.5 Histology of staphylococcal scalded skin syndrome: subcorneal bullous cavity (hematoxylin and eosin, ×200). (Courtesy of Carlo Gelmetti, Milan, Italy.)

fresh lesions do not harbor staphylococci. In the full-blown disease, shock is a typical feature, whereas postural dizziness may be an important diagnostic clue in the early stages or mild cases.

The main differential diagnosis includes TEN, which usually affects adults and is uncommon in children. In this severe drug-induced reaction, the skin changes are widespread, and severe mucosal involvement is common (erosive mucositis is part of the clinical presentation in TEN), whereas SSSS extends from the face and flexures and does not affect mucosae with erosions. Histologically, TEN shows subepidermal splitting, also in frozen sections, with full-thickness necrosis of the epidermis, whereas SSSS is characterized by subcorneal cleavage with a viable appearance of the epidermis. The two conditions can be rapidly differentiated by means of exfoliative cytology. A Tzanck smear taken from a fresh bulla shows necrotic keratinocytes with inflammatory cells in TEN and viable acantholytic or normal keratinocytes without inflammatory cells in SSSS, but accurate interpretation requires an experienced observer. Other differential diagnoses comprise Leiner and Kawasaki diseases. Leiner disease, the erythrodermic form of seborrheic dermatitis in newborns, lacks blisters or erosion, but yellowish scales are present all over the body. Prolonged fever, heart involvement, and generalized lymphadenopathy characterize Kawasaki disease. Slide latex agglutination, double immunodiffusion, and enzyme-linked immunosorbent assay tests—which can identify the staphylococcal toxins responsible for the intraepidermal splitting—are all useful in confirming a SSSS clinical diagnosis.

COURSE AND PROGNOSIS

The disease in newborns (Ritter disease) is usually self-limiting, with rapid resolution of the skin blisters and complete recovery in a couple of weeks, but there is a mortality of 2%–3% due to progression of the staphylococcal infection (sepsis) or exfoliative complications (serious fluid and electrolyte disturbances). In children, with appropriate treatment, complications (cellulitis, pneumonia) are uncommon, and the prognosis is usually good, with a low mortality risk (about 5%). In adults, SSSS carries a less favorable prognosis due to basic medical problems, such as immunosuppression or kidney failure. Adults are much more likely than children to develop staphylococcal sepsis, which brings the mortality rate to more than 50%, despite appropriate antimicrobial therapy.

MANAGEMENT

Patients with SSSS require hospitalization because, besides the appropriate systemic antimicrobial therapy, intensive general supportive measures are needed. Treatment options of SSSS are resumed in Table 11.2. The mainstay of treatment is the eradication of staphylococci from the focus of infection, which in most cases requires intravenous (IV) antistaphylococcal antibiotics (e.g., methicillin, flucloxacillin). Subsequently, parenteral therapy may be replaced with 1-week oral treatment with a β -lactamase-resistant antibiotic (e.g., dicloxacillin, cloxacillin, cephalexin). Second-line therapies include an IV macrolide (erythromycin or clarithromycin)¹¹ or vancomycin.¹² Due to the disrupted cutaneous barrier function, which may lead to dehydration and electrolyte imbalance, IV replacement of fluids and lacking electrolytes is recommended for prompt recovery.

Table 11.2 Management of Staphylococcal Scalded Skin Syndrome

Infection	Systemic penicillinase-resistant antibiotic (Flucloxacillin)
	<ul style="list-style-type: none"> • Children (50–100 mg/kg/die) • Adults (500–1000 mg/die) <p>In case of penicillin allergy: clarithromycin or cefuroxime In case of methicillin-resistant <i>Staphylococcus aureus</i>: vancomycin Fresh frozen plasma (10 mL/kg) to neutralize exotoxin in children Intravenous immunoglobulin (0.4 g/kg/day for 5 days)</p>
Pain	<ul style="list-style-type: none"> • Acetaminophen • Midazolam • Opiates (Fentanyl)

In each case, oral fluid intake and careful monitoring of urinary output should be encouraged. If required, analgesics should be used. The superficial nature of the erosions in SSSS paves the way to rapid reepithelialization following appropriate topical therapy. The therapy consists of nonirritant, nonsensitizing antiseptics (e.g., 1:1000 diluted aqueous potassium permanganate solution) on denuded, moist areas and bland, lubricating emollients on itching, tender, scaling areas. Newborns with SSSS should be kept in incubators to maintain body temperature. In neonatal care units, as well as elsewhere in the health facility where there are patients with hospital-acquired cases of SSSS, it is of the utmost importance to identify health-care workers who are possible carriers of toxigenic staphylococci. Useful preventative measures encompass strict enforcement of chlorhexidine hand washing, oral antimicrobial treatment for infected workers, and the use of intranasal mupirocin ointment to eradicate persistent nasal carriage of toxigenic strains of *S. aureus*.²

FUTURE PERSPECTIVES

The increasing frequency of methicillin-resistant *S. aureus* (MRSA) strains raises the possibility that antibiotic-resistant, ET-producing staphylococci can become pathogens in future cases of SSSS. The development of innovative, alternative therapies may rapidly become an urgent necessity. Structural identification of the dsG 1 binding site of staphylococcal ETs and the generation of neutralizing antibodies that efficiently inhibit the reaction between enzyme and substrate will provide a novel therapeutic option for SSSS caused by MRSA.⁷

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Life-threatening cutaneous viral diseases

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Viral diseases frequently have cutaneous manifestations, most of which are self-limited and of little consequence; however, there are occasions when a viral cutaneous disease may be accompanied by systemic manifestations that can be life threatening. In general, healthy children and adults are at little risk for these severe complications. Persons at highest risk for systemic involvement include patients who are immunosuppressed, as well as neonates, extremely elderly persons, and the undernourished population. Because many viruses have some form of cutaneous exanthem, almost any virus known to have systemic involvement can be considered a dermatologic emergency. This chapter focuses mainly on those viruses in which the cutaneous findings would be likely to prompt dermatologic investigation in an emergency situation.

HERPES SIMPLEX VIRUS

Presentation and Clinical Features

Herpes simplex virus (HSV) is not typically associated with life-threatening or emergency situations; rather, HSV is better known as an acute, self-limited infection that may recur in certain individuals. In rare instances, fatal and highly morbid complications can arise. Neonates and immunocompromised persons generally make up the vast majority of patients with these poor outcomes, but in extremely rare cases, some immunocompetent patients suffer severe complications.

HSV can be divided into two subgroups (HSV-1 and HSV-2) based on molecular and immunologic characteristics. HSV-1 typically causes lesions in the oral mucosa and produces gingivostomatitis and pharyngitis in primary infections, but is also commonly asymptomatic. Primary infections of HSV-2 most commonly cause genital lesions and produce acute vulvovaginitis and proctitis. Despite tropism to these anatomical locations, both strains can affect either site. Several studies have shown that about 60%–78% of incident genital herpes may now be attributable to HSV-1.¹ Historically, infection with HSV-1 generally occurred during childhood, whereas HSV-2 was acquired after puberty in individuals who engaged in sexual contact; however, recent studies have shown that childhood acquisition of HSV-1 has declined with a subsequent increase in serosusceptible adolescence and young adults.¹ This lack of immunity combined with increased oral sex behavior in young people may lead to increased likelihood of primary genital HSV-1 infection.¹

The classic HSV presentation is indurated erythema followed by grouped vesicles on an erythematous base. These vesicles eventually become pustules, which rupture and eventually crust. Sometimes, the affected skin may become necrotic and result in a punched-out ulcerative appearance. Clinical manifestations, however, can vary and

include acute gingivostomatitis, herpes labialis, ocular herpes, herpes genitalis, zosteriform herpes simplex, herpetic whitlow, eczema herpeticum, meningitis, encephalitis, visceral infections, and neonatal herpes. Both HSV-1 and HSV-2 are associated with recurrent infections in patients with low immunologic status.

Neonatal HSV

HSV is known to infect the neonate in approximately 1 in 3200 deliveries.² Transmission to the neonate can occur by intrauterine (5%), intrapartum (85%), or postpartum (10%) infection.^{3–7} The risk of neonatal herpes is greatest if a woman has a primary occurrence at delivery, lower if she has a recurrent episode, and lowest if there is a history of HSV but no lesions at delivery.² Although cesarean section has proven to be effective in decreasing the chances of HSV transmission to the neonate from a mother actively shedding virus from the genital tract, the majority of transmitted infections arise from mothers who do not have lesions at the time of delivery. Approximately 60%–80% of women who deliver an HSV-infected infant have no evidence of genital HSV infection at the time of delivery, no past history of genital herpes, or no sexual partner reporting a history of genital HSV.^{2,8–10}

In neonates, HSV can manifest in three different types of infections (Table 12.1).

Neonatal disseminated HSV infection and central nervous system (CNS) HSV disease both have high mortality rates without treatment. In those individuals who do survive without treatment, significant neurologic impairment is common.^{8,11} Although skin, eye, and mouth HSV neonatal infections typically do not cause mortality, without antiviral therapy, approximately 75% of infections will eventually develop into CNS or disseminated disease.⁸

HSV in Immunocompromised Patients

Higher mortality rates and more severe recurrent episodes of HSV have been associated with immunocompromised individuals. These patients should also be monitored for dissemination and/or CNS involvement in HSV infections. This includes patients with human immunodeficiency virus (HIV), recipients of organ transplantations, pregnant women, or patients with any other disease/state that affects T-cell function. Patients with defects in natural killer (NK) cell function are also particularly susceptible to severe and disseminated herpesvirus infections including HSV, but also cytomegalovirus, varicella zoster virus, and Epstein–Barr virus.¹³

HSV-2 is also a significant risk factor for HIV transmission due to compromised skin integrity as well as increases in HIV-susceptible CD4⁺ T cells. Thus proper control may help decrease HIV transmission rates.¹⁴

Table 12.1 Herpes Simplex Virus in Neonates

Type of neonatal HSV infection	Incidence ⁸	Mortality without treatment ^{8,11}	Presentation ¹²	Therapy ²⁷	Onset ^{27,28}
Skin, eye, and mouth infections	45%	0%	Discrete vesicles and keratoconjunctivitis to spastic quadriplegia, microcephaly, and blindness	IV acyclovir 20 mg/kg every 8 h for 14–21 days	10–11 days
Central nervous system	35%	50%	Seizures, lethargy, irritability, tremors, poor feeding, temperature instability, bulging fontanelle, or pyramidal tract signs	60 mg/kg/d in three divided doses for 21 days is advised	16–19 days
Disseminated multiorgan infection	20%	80%	Irritability, seizures, respiratory distress, jaundice, bleeding diatheses, shock, and vesicular exanthema	60 mg/kg/d in three divided doses for 21 days is advised	9–11 days

Notes: HSV, herpes simplex virus; IV, intravenous.

Herpes Simplex Encephalitis

Herpes simplex encephalitis (HSE) is the most commonly identified cause of acute, sporadic viral encephalitis in the United States, comprising 10%–20% of all cases.¹⁵ It is estimated to have an incidence of approximately 1 case per 250,000 population per year.¹⁶ Mortality in untreated patients is in excess of 70%, and only 2.5% of all patients recover full neurological function. The pathology of HSE varies and may occur in a primary or recurrent infection. Not all cases have skin lesions, and differentiation from other encephalitides can be very difficult. HSV DNA in the cerebrospinal fluid confirmed by polymerase chain reaction is the most sensitive noninvasive test for early diagnosis.¹⁷ HSE manifests as an acute onset of fever and focal (temporal) neurologic symptoms.¹⁸ Patients typically complain of headache, nuchal rigidity, weakness, sensory abnormalities, aphasia, visual field defects, or cranial nerve palsies.¹⁹

Eczema Herpeticum

Eczema herpeticum is a potentially life-threatening dermatologic emergency that involves a herpetic superinfection of a preexisting skin disease. It is most commonly seen in individuals who have disruptive skin diseases (typically atopic dermatitis) or are immunocompromised (secondary to topical steroids for skin disease). It is commonly seen in children of all ages and all ethnic groups, with the highest incidence occurring in children under 4 years.²⁰ Without rapid antiviral therapy, complete dissemination can occur, leading to fulminant hepatitis and possible death.^{21,22}

Eczema herpeticum is similar to the classic skin lesions of HSV except that there are multiple clusters of vesicles in areas of previous skin disease involvement along with systemic symptoms (fever and malaise). Vesicles spread and result in punched-out erosions causing significant pain. Lesions may be discrete or confluent, and tend to occur in crops, resulting in many lesions at different stages.²³ Other signs and symptoms may include pruritus, vomiting, anorexia, diarrhea, lymphadenopathy, and/or secondary bacterial infection.^{24,25}

Visceral Infections

The most common sites of visceral infections are the esophagus, lung, and liver; the infections usually result from viremia. Of these, lung and liver infections have the worse prognoses. Lung HSV infections frequently present as a focal necrotizing pneumonitis and are more common in severely immunocompromised patients. Mortality is considered to be greater than 80%.

HSV hepatitis also has a high association with mortality (near 80%) and can present with fever, abdominal or right

upper quadrant pain, nausea and vomiting, abrupt elevations of bilirubin and serum aminotransferase levels, and leukopenia.²⁶ HSV hepatitis has been seen in immunocompetent and immunosuppressed persons.

Prevention and Treatment

For treatment of mucocutaneous infections:

- The mainstay of HSV therapy is the synthetic purine nucleoside analogues acyclovir, valacyclovir, famciclovir, and penciclovir.
- In emergency situations, intravenous (IV) acyclovir (5 mg/kg every 8 hours) should be used.

HSV in a neonate is considered a pediatric emergency, and antiviral therapy should be initiated as soon as there is clinical suspicion.²⁷

- IV acyclovir is highly recommended for all cases of neonatal HSV. Treatment of neonatal HSV with IV acyclovir is described in Table 12.1.
- For maximum benefit, antiviral therapy must be administered before widespread dissemination or significant replication of the virus in the CNS has occurred.²⁸
- Dosing intervals for IV acyclovir should be increased in premature infants due to their high creatinine clearance.²⁹ In rare cases, IV acyclovir has been associated with neutropenia and nephrotoxicity; therefore, neutrophil counts and kidney function should be monitored in neonates when receiving IV acyclovir.²⁷ With acyclovir therapy, the mortality of disseminated HSV and CNS HSV is reduced to 29% and 4%, respectively.²⁷
- Preventing maternal primary infection is of the utmost importance, because primary infection has the highest rate of transmission to the infant. To prevent maternal infection, condoms or suppressive oral acyclovir in late pregnancy has been beneficial for persons who are in sexual contact with partners who have genital herpes.

In immunocompromised patients:

- Systemic treatment with antiviral therapy such as acyclovir should be started.
- For patients who may have acyclovir-resistant HSV, foscarnet can be used, but it is generally reserved for patients with extensive mucocutaneous infections due to its high cost and toxicity.³⁰

- Cidofovir has also been proven to work as a topical medication for HSV lesions and may also be used in acyclovir-resistant patients.

Prompt treatment is of the utmost importance to prevent the high mortality associated with HSE.

- It is recommended that HSE patients be treated with IV acyclovir at 5–10 mg/kg every 8 hours for 14–21 days.³¹ Renal adjustments to dosage should be made.
- Even in presumed HSE, IV acyclovir is recommended until an alternative diagnosis is made, and continued when the diagnosis of HSE is confirmed.³²

For visceral HSV infections:

- IV acyclovir is recommended.
- In some cases, liver transplant plus high-dose acyclovir therapy have been used to treat fulminant HSV hepatic failure.^{33,34}

VARICELLA ZOSTER VIRUS

Presentation and Clinical Features

Primary Varicella

Varicella zoster virus (VZV) presents as chickenpox (varicella) as a primary infection and shingles (herpes zoster) when the virus is reactivated. Varicella is generally a self-limited disease, usually of childhood, that causes outbreaks of vesicles and pustules classically described as “dewdrops on a rose petal.” Lesions progress from a vesicle into a pustule that then produces an itchy scab. Classically, all of these stages are present simultaneously, as the lesions develop in successive crops. Varicella is common, as more than 95% of adults in the United States have antibodies to the virus. In healthy children, the mortality rate is quite low, estimated at two deaths per 100,000 cases.³⁵ In immunocompromised patients and neonates, however, complications such as pneumonitis, thrombocytopenia, liver function impairment, and CNS involvement are more common and must be recognized and treated promptly.

Neonatal varicella is mostly caused by maternal chickenpox acquired during the last 3 weeks of pregnancy. Death may occur due to complications of generalized neonatal varicella in up to 20% of neonates if the mother develops a rash between days 4 and 5 antepartum to day 2 postpartum.³⁶ Whereas neonatal chickenpox occurring within the first 4 days after birth tends to be mild, a fatal outcome has been reported in 23% of cases occurring between 5 and 12 days of age.³⁶

Primary varicella in adults is frequently more severe than in children. Fewer than 5% of cases of varicella occur in adults; yet, 55% of varicella-related deaths occur in this age group, usually due to pneumonia and consequent respiratory failure.^{35,37}

Herpes Zoster

Herpes zoster has a lifetime incidence between 10% and 25%, with the elderly population being at greater risk than the general population. Like varicella, herpes zoster is rarely life threatening in immunocompetent people. The disease is recognized by dermatomal pain and a vesicular eruption. Pain may be intense and can last for months after the eruption heals (postherpetic neuralgia). Herpes zoster is generally limited to a single dermatome or a few adjacent dermatomes but may disseminate, particularly in

patients with immunosuppression due to HIV, hematologic malignancy, organ transplantation, or chemotherapy. Disseminated zoster results from hematogenous spread of the virus, resulting in involvement of multiple dermatomes, as well as potentially systemic involvement. Dissemination is life-threatening due to the potential to cause encephalitis, hepatitis, or pneumonitis.

Disseminated herpes zoster may present with visceral symptoms including hepatitis, pancreatitis, gastritis, or abdominal pain. Occasionally, these complaints are seen even without skin involvement at all, or can be the presenting feature before a rash develops.^{38,39} CNS involvement may be seen in the form of cranial nerve palsies or encephalitis in up to one third of patients with disseminated zoster.⁴⁰

Although the incidence of shingles among recipients of solid organ transplants is approximately 9%,³⁵ the complications of dissemination in these patients are particularly grave. A review of the literature of disseminated varicella infection in adult renal allograft recipients found a mortality rate of 34%.⁴¹ Use of mycophenolate mofetil (a drug commonly used to prevent organ transplant rejection) has been associated with increased susceptibility to VZV infection.⁴²

Of note, disseminated herpes zoster is not limited to immunocompromised persons. Although rare, there have been reported cases of disseminated cutaneous herpes zoster without any apparent immunosuppression. It has been proposed that significant age-related depression in cellular immunity can contribute to dissemination of herpes zoster; therefore, elderly patients should be recognized as a group in which dissemination risk is higher than the average immunocompetent host.⁴³

Prevention and Treatment

Treatment for classic herpes zoster may be given orally with

- Acyclovir (800 mg five times a day for 7–10 days)
- Valacyclovir (1000 mg three times a day for 7 days)
- Famciclovir (500 mg three times a day for 7 days)

The treatment of choice for disseminated zoster is

- IV acyclovir 10 mg/kg every 8 hours for 7 days⁴³

To reduce the incidence of postherpetic neuralgia in patients with herpes zoster:

- An antiviral, such as valacyclovir, should be given with gabapentin. This combination therapy should be administered acutely, rather than waiting for chronic pain to develop.⁴⁴

For primary varicella in immunocompromised populations:

- IV acyclovir (10 mg/kg every 8 hours) should be given.

To prevent severe neonatal chickenpox in seronegative mothers exposed to VZV:

- Administration of varicella immune globulin for passive immunization is indicated.³⁶

A live, attenuated varicella zoster vaccination has been approved by the U.S. Food and Drug Administration (FDA) for prevention of varicella in children since 1995, and a similar vaccine to prevent herpes zoster outbreaks in adults received

approval in 2006. While vaccination is the cornerstone of prevention, it is contraindicated in pregnancy and in the immunocompromised. Disseminated zoster after vaccination has been reported in cases of patients undergoing chemotherapy, with acquired immune deficiency syndrome (AIDS), and even in a novel deficiency in natural killer T cells.^{45–47} These multiple reports of disseminated infection resulting from the Oka vaccine strain in immunocompromised patients point to the need for careful medical history taking prior to vaccination to avoid vaccinating patients who are immunosuppressed.

SMALLPOX (VARIOLA MAJOR) AND VACCINIA Presentation and Clinical Features

Smallpox was, historically, one of the most lethal viruses known to man until it was eradicated in 1980 by a worldwide vaccination effort.⁴⁸ The last reported case of smallpox was in 1977; therefore, a significant percentage of the world's population is susceptible to smallpox infection.³⁵ Unfortunately, in the modern era, the potential use of smallpox as a weapon of bioterrorism makes this virus of continued interest to dermatologists.

Smallpox is spread by the respiratory route and has a prodromal phase of high fever, headache, and backache. Skin lesions are classically distributed in a centrifugal pattern with greater involvement of the face and extremities than of the trunk. Lesions begin as erythematous macules, which then evolve in synchrony (as opposed to chickenpox) into papules, pustules, and then crusts with the entirety of the rash lasting approximately 2 weeks. Mortality from smallpox infection is approximately 30%.⁴⁹

Prevention and Treatment

Smallpox was eradicated due to vaccination. The vaccinia virus is used to vaccinate against smallpox and produces a localized exanthem at the site of inoculation. The virus is inoculated through multiple punctures into the upper dermis. Persons with severe cell-mediated immunodeficiency should not receive the vaccination due to potential complications of encephalitis, generalized vaccinia (a self-limited eruption), progressive vaccinia, or accidental infection. Vaccinia necrosum is characterized by failure of the vaccination site to heal, followed by progressive necrosis and ulceration that may or may not spread to distant sites (skin, bones, and viscera).⁵⁰ Untreated progressive vaccinia can be fatal and should be treated with systemic vaccinia immune globulin (VIG) and sometimes thiosemicarbazone.⁵¹ Generalized and progressive vaccinia are uncommon complications in the absence of immunosuppression, and thus most cases occur in patients with undiagnosed immunodeficiency. Transmission of vaccinia following vaccination is possible, although the transfer rate is low if the vaccination site is kept covered until it heals. Vaccination against smallpox is no longer commonplace, although the possibility of reinstituting a vaccination program is being considered due to the high susceptibility of the world's population and potential use as biological warfare.

PARVOVIRUS B19 Presentation and Clinical Features

Parvovirus B19 (PVB 19), a small single-stranded DNA virus from the family Parvoviridae, is a virologic pathogen that often causes asymptomatic infection but may become life threatening in certain circumstances. The common dermatologic manifestations associated with PVB 19 infection include erythema infectiosum, papular purpuric "gloves-and-socks" syndrome,

and nonspecific findings such as reticular erythema, petechiae, and/or purpura, and maculopapular eruptions.

Erythema infectiosum, otherwise known as fifth disease, is common in the pediatric population and is characterized by the classic "slapped-cheek" facial erythema and the fine reticulated (lacy) erythema involving the trunk and extremities. Papular purpuric "gloves-and-socks" syndrome is a disease seen in adulthood, which presents with the hallmark symmetric, sharply demarcated erythema and edema of the hands and feet that evolves into petechiae and purpura over time. Patients with PVB 19 may also manifest acute nondegenerative arthritis and arthralgia.

Although PVB 19 infections are often mild and self-limited, patients who are immunosuppressed, have hematologic diseases, or are pregnant are at risk for serious complications. PVB 19 infects erythroid progenitor cells and temporarily halts red blood cell production, thereby causing a transient aplastic crisis (TAC). Individuals with hematologic conditions such as sickle cell anemia, thalassemia, autoimmune hemolytic anemia, and other similar conditions are at increased risk for developing an aplastic crisis. Often the crisis is transient and self-resolving, but the risk of a fatal complication increases in this subset of patients. Immunocompromised individuals lack the ability to mount an immune response to the virus and may have a course complicated by lingering cutaneous eruptions, persistent anemia, myocarditis, pericarditis, acute heart failure, acute liver failure, meningitis, and encephalitis.⁵² Because these patients mount a decreased immune response, they may not manifest the characteristic immune-mediated eruption and joint findings.⁵³

Maternal parvovirus infection during pregnancy can lead to vertical transmission of the virus to the unborn fetus. The incidence of maternal PVB 19 infection during pregnancy is 1%–2%, with vertical transmission occurring in 33%–51% of cases,^{54–56} and fetal loss occurring in approximately 10% of all cases.^{57,58} Fetal infection can result in miscarriage or non-immune hydrops fetalis. The incidence of fetal morbidity and mortality is inversely related to gestational age; thus, infection during the first trimester is the most dangerous.

Prevention and Treatment

The treatment for PVB 19 is mostly symptomatic, and immunocompetent patients do very well. Immunocompromised patients, pregnant women, and persons with hematologic disease must be closely monitored by their respective specialists.

In patients with transient aplastic crisis:

- Transfusion for severe anemia may be required until the infection is eliminated.

If infection occurs during pregnancy with severe fetal anemia:

- Intrauterine transfusion can correct fetal anemia and reduce fetal death. The procedure is generally done after 18 weeks because of technical limitations but before 35 weeks because of excessive fetal risk compared to delivery.^{59,60}

In chronic PVB 19 with anemia:

- High-dose IV immunoglobulins (400 mg/kg/day for 5 days or 1000 mg/kg/day for 3 days) have been shown to eliminate the virus from the bone marrow.

Prevention is difficult because, when a patient presents with a rash, he or she is no longer contagious; thus no measures can be taken to avoid infecting others.^{54,61}

CYTOMEGALOVIRUS

Presentation and Clinical Features

Cytomegalovirus (CMV, human CMV [HCMV], or human herpesvirus [HHV]-5) is a large double-stranded virus from the herpesvirus family. Most commonly, CMV mononucleosis is mild and asymptomatic, with no impact on the immune system. Immunocompromised individuals, such as those with HIV or a malignancy, or those who have had an organ transplant, may exhibit complications with CMV infection. Blood transfusion recipients and newborns are other patient populations that may have a lethal outcome from a CMV infection.

CMV infections are a frequent cause of morbidity and mortality among immunocompromised patients. The virus itself may not directly lead to the death of a patient, but it further lowers the patient's immune system, thus making him or her much more susceptible to other deadly diseases. For example, patients with HIV may die from a coinfection with CMV and *Pneumocystis carinii* (now renamed *Pneumocystis jirovecii*). Prognosis depends on the extent and interval of immunosuppression. CMV infection may increase the rate of organ rejection by inducing autoantibodies.⁶² Patients with postperfusion syndrome (CMV mononucleosis acquired via blood transfusion) exhibit fever, malaise, hepatosplenomegaly, and jaundice; these patients carry a poor prognosis.⁶³

Newborns can acquire CMV in utero (transplacentally), after exposure to genital secretions in the vaginal canal, or through breastfeeding.⁶⁴ Severe clinical manifestations of congenital CMV infection most often occur when the mother sustains a primary CMV infection rather than reactivation of a recurrent infection. The disease tends to be more severe if the infection is acquired earlier in gestation. The dermatologic manifestations of CMV infection include petechiae, purpura, jaundice, and "blueberry muffin" syndrome. Even if a newborn is born without overt symptoms, he or she is at risk for long-term complications such as hearing loss and/or mental retardation. About 5%–10% of neonates will die of multiorgan failure.⁶⁵

Prevention and Treatment

Treatment of immunocompromised patients may require two phases—an induction phase followed by a maintenance phase for high-risk patients.

- Ganciclovir is used in both induction and maintenance therapy.
- Oral valganciclovir is an alternative for maintenance therapy.
- Patients may also be given hyperimmune globulin (HIG) as passive immunization.

Little can be done in terms of prevention of CMV infection. This is especially problematic for transplant patients. To help prevent infection in these patients:

- IV ganciclovir or high-dose acyclovir are given.
- HIG may be given.
- Patients should also undergo frequent monitoring using polymerase chain reaction (PCR).

In pregnancy, prevention of CMV infection starts with hygienic behavior for seronegative women.

- Pregnant women with primary CMV infection may be given passive immunization with hyperimmune globulin (HIG); however, this is not generally recommended, as studies have shown mixed results and patients who receive HIG may have higher adverse obstetrical events.^{66–68}
- Ganciclovir can be used safely and effectively in newborns. The efficacy of ganciclovir in pregnancy is unknown, and there is concern about possible teratogenic effects on the fetus.
- Pregnancy termination is an option, if fetal infection is diagnosed via ultrasonography or amniocentesis.⁶⁹
- No drugs have been shown to prevent perinatal transmission.

Although there have been several CMV vaccine candidates, none have been approved yet.

MEASLES (RUBEOLA)

Presentation and Clinical Features

The first sign of measles infection is usually high fever (approaching 40°C at its peak) beginning approximately 10–12 days after exposure and lasting 1–7 days. Other associated symptoms include coryza, conjunctivitis, and cough. Approximately 2–3 days later, a cutaneous exanthem appears, consisting of an erythematous eruption composed of macules and papules (usually beginning on the face and upper part of the neck) that coalesce and spread to the trunk and eventually to the extremities, hands, and feet. Often, there is a diagnostic enanthem of bluish-gray areas on the tonsils (Herman spots) and punctate blue-white lesions surrounded by an erythematous ring on the buccal mucosa (Koplik spots).⁷⁰ The exanthem lasts for 5–6 days, then fades, whereas the enanthem occurs a few days prior to the exanthem and lasts 2–3 days.

For most persons, measles is an unpleasant mild or moderately severe illness. In poorly nourished young children, however, especially those who do not receive sufficient vitamin A, or whose immune systems have been weakened by HIV/AIDS or other diseases, severe complications including blindness, encephalitis, severe diarrhea (which can cause dehydration), pneumonia, and mortality from such complications can result.^{71,72}

Encephalitis is estimated to occur in 1 of 800–1000 cases (although death and brain damage are limited to a small minority of cases), whereas pneumonia may occur in 5%–10% of cases. More uncommon is subacute sclerosing panencephalitis, which can develop in approximately 1 of 100,000 cases and cause mental and motor deterioration, seizures, coma, and death.³⁵

Overall, the case fatality rate in developing countries is generally in the range of 1%–5%, but may be as high as 25% in populations with high levels of malnutrition and poor access to health care. In January 2007, the World Health Organization/United Nations Children's Fund (WHO/UNICEF) reported that implementation of measles mortality reduction strategies (including vaccinations and early treatment strategies) had reduced measles mortality by 60%, from an estimated 873,000 deaths worldwide in 1999 to 345,000 deaths in 2005.^{73,74}

Prevention and Treatment

When treating patients with measles, severe complications can usually be avoided.

- General nutritional support and the treatment of dehydration with oral rehydration solution are necessary.
- Should eye and ear infections or pneumonia result, antimicrobials may be prescribed.
- In developing countries, persons diagnosed with measles should receive two doses of vitamin A supplements, given 24 hours apart to help prevent eye damage and blindness. More importantly, vitamin A supplementation has been shown to reduce the number of deaths from measles by 50%.⁷⁵

The best weapon we have against measles is vaccination to prevent disease. The measles vaccine is a live attenuated vaccine that first became available in 1963. In the United States, it is generally given as part of either the measles, mumps, rubella (German measles) (MMR) or MMR plus varicella (MMRV) vaccines. The vaccine is given in two shots, the first at 12–15 months and the second at 4–6 years of age.⁷⁶ After the second shot, approximately 99% of people become immune to the disease. Because it is a live vaccine (like the varicella vaccine), immunocompromised patients and those who are pregnant should not be vaccinated. An increase in vaccine exemptions has led to a resurgence of the disease with a record number of cases reported since declared eliminated from the United States in 2000.^{77,78}

GERMAN MEASLES (RUBELLA) Presentation and Clinical Features

Rubella tends to be milder than rubeola. Often called 3-day measles due to the duration of its classic eruption, it is recognized by mild constitutional symptoms, followed by an erythematous eruption that begins on the face and spreads from head to foot. Unlike measles, the rash of rubella is nonconfluent and tends to have a lesser degree of erythema. Additionally, petechiae of the palate may be present. In general, rubella is uncomplicated, but infection during pregnancy can lead to congenital rubella syndrome (CRS), an important cause of severe birth defects.⁷⁹ When a woman is infected with the rubella virus early in pregnancy, she has a greater than 50% chance of passing the virus on to her fetus, which may cause fetal demise or CRS, whereas infection later in pregnancy has a lower risk of CRS.⁸⁰ Common birth defects that may occur due to CRS are ocular defects, cardiovascular defects, CNS defects, deafness, microcephaly, mental retardation, and intrauterine growth retardation.

An uncommon but important systemic complication, particularly in adult women, is encephalitis. Rubella encephalitis occurs in approximately 1 in 6000 cases and is fatal in approximately 20% of these cases.⁸¹

Prevention and Treatment

The currently used rubella vaccine is a live attenuated strain that was developed in 1979 and is given as part of the MMR or MMRV vaccine. The vaccine schedule includes a first shot at 12–15 months and a second at 4–6 years of age.⁷⁶ As it is a live virus vaccine, immunosuppressed patients should not be vaccinated. Treatment for rubella infection is supportive.

MOSQUITO-BORNE VIRUSES Presentation and Clinical Features

Mosquitoes have been called the world's deadliest animals, as diseases spread by these insects are responsible for more deaths than all mammals, amphibians, reptiles, birds, and fishes combined. Three such life-threatening viral diseases of concern to dermatologists include dengue, yellow fever, and West Nile virus.

Dengue causes fever as well as headache, retro-orbital pain, myalgia, and arthralgia that may be followed by a skin eruption in up to 80% of patients during the remission of the fever. The eruption classically consists of a mild macular eruption over the nape of the neck and face lasting up to 5 days. Petechiae or purpura, as well as involvement of the palms and soles followed by desquamation and proximal spread to the arms, legs, and torso, are also common.^{35,79} This eruption is helpful diagnostically, as prior to the eruption, the differential can include malaria, yellow fever, and influenza.³⁵ Dengue is associated with two life-threatening complications: hemorrhagic fever and shock syndrome. Hemorrhagic fever consists of a sudden temperature elevation lasting 2–7 days followed by bleeding from sites of trauma as well as the GI tract and urinary tract. The average case fatality is approximately 5%,³⁵ but in severe cases of dengue, hemorrhagic fever mortality may reach 50%.⁷⁹ Occasionally, shock syndrome may follow hemorrhagic fever. In these cases, circulatory and respiratory failure may occur, resulting in death in approximately 2% of cases.

Yellow fever has two disease phases. The first (acute phase) presents with fever, muscle pain (especially backache), headache, anorexia, and nausea and/or vomiting. Most patients improve after 3–4 days.⁸² Approximately 15% of patients will enter a toxic phase consisting of fever reappearance, jaundice, and abdominal pain. Hemorrhage from the GI tract, mouth, nose, and eyes may occur. Liver and kidney failure may occur, and mortality can be as high as 40% in this toxic phase because of hepatorenal failure.⁷⁹ Dermatologic findings in yellow fever include icteric skin (hence the name “yellow” fever) as well as hemorrhages or petechiae of the skin and mucous membranes.

West Nile virus can cause fever, headaches, GI symptoms, and (in up to 50% of cases) a skin eruption characterized by punctate, erythematous macules, and papules most pronounced on the extremities.^{35,79} Common serious complications include meningitis, encephalitis, and flaccid paralysis, although less than 1% of infections result in severe neurological illness. Persons at greatest risk for neurologic disease are those older than 50 years.

Prevention and Treatment

There are currently no antiviral treatments for the mosquito-borne viruses. Treatment for dengue and yellow fever is symptomatic, consisting of rehydration, rest, analgesia, and antiemetics, whereas therapy for West Nile virus is the same as for patients with meningoencephalitis.⁷⁹

Vaccination is available for yellow fever and is recommended every 10 years for persons visiting endemic countries.^{79,83} There are no currently available vaccines for dengue or West Nile virus. The best form of prevention is to avoid mosquito bites. Using insect repellent; getting rid of mosquito breeding sites by emptying standing water from flower pots, buckets, or barrels; staying indoors between dusk and dawn (when mosquitoes are most active); and using screens on windows to keep mosquitoes out are all effective techniques.

MARBURG AND EBOLA VIRUSES

Presentation and Clinical Features

The Filoviruses, Marburg and Ebola, cause severe hemorrhagic fever in human and nonhuman primates. The classic eruption that may bring these infections to dermatologic attention is a nonpruritic centripetal eruption composed of macules and papules with varying degrees of erythema.⁸⁴ The eruption occurs approximately 2 weeks after exposure and tends to desquamate by day 5 or 7 of the illness. Hemorrhagic manifestations include GI tract bleeding, bleeding into the oropharynx and lungs, petechiae, hemorrhage from puncture wounds, and massive gingival bleeding.⁸⁴ Mucosal bleeding and persistent vomiting are ominous symptoms in these diseases. Mortality due to Marburg and Ebola ranges between 30% and 90%, depending on the strain of the virus.^{85,86}

Prevention and Treatment

Currently, there is no approved virus-specific treatment for either Marburg or Ebola virus; therefore, supportive therapy is the standard of care. When caring for infected patients:

- Maintain effective blood volume and electrolyte balance in hemorrhaging patients.⁸⁴
- Appropriately manage any shock, cerebral edema, renal failure, coagulopathy, and secondary bacterial infection, which are commonplace in these patients.
- Isolation is recommended to prevent spread of the disease to additional patients. When available, patients should be placed in a negative pressure room if experiencing symptoms of cough, vomiting, diarrhea, or hemorrhage.⁸⁷

Experimental drugs and methods have been used to treat Ebola on a compassionate basis including

- Favipiravir and brincidofovir (antiviral medications)
- ZMapp (a composition of monoclonal antibodies)
- TKM-Ebola (a combination of small interfering RNAs targeting the Ebola proteins)
- Transfusion of convalescent plasma and blood^{88,89}

HUMAN IMMUNODEFICIENCY VIRUS

Presentation and Clinical Features

First described in 1981, human immunodeficiency virus (HIV) is a lentivirus that causes acquired immunodeficiency syndrome (AIDS) in which declining immune function leads to opportunistic infections (OIs) and cancers. The virus is transmitted through perinatal exposure, sexual intercourse, and infected blood. Untreated, HIV progresses to a significant reduction in cell-mediated immunity that is manifested by low CD4 counts. While infection with HIV itself is not an emergency, the virus predisposes patients to more frequent and severe opportunistic infections that may be life threatening. Such fungal, bacterial, and viral infections may have cutaneous manifestations. This includes infections with *Coccidioides immitis*, which may disseminate and present with dermatologic findings including nodules, plaques, ulcers, and pustules that are often hemorrhagic.⁹⁰ Patients with *C. immitis* infection may also develop erythema nodosum or erythema multiforme.^{90,91} The bacterium *Pneumocystis jiroveci* is another important opportunistic infection, which may present with cutaneous manifestations, such as macular, polypoid, or

molluscum contagiosum-like lesions.⁹² Viruses, such as HSV, CMV, and varicella zoster which do not usually cause serious disease in healthy immunocompetent patients, may lead to life-threatening infections in HIV-positive patients as discussed above.

HIV-positive patients are also at higher risk for adverse cutaneous drug reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Patients may be predisposed to developing these reactions due to loss of cutaneous T-cell function.⁹³ SJS and TEN also put patients at increased risk for systemic bacterial infection, a major cause of mortality in such reactions.^{93,94}

Prevention and Treatment

Treatment of HIV and associated opportunistic infections begins with the initiation of antiretroviral therapy (ART) if patients are not already on a regimen. Current standards of treatment indicate for all patients with HIV to be on ART regardless of CD4 counts.⁹⁵ Early initiation of ART in patients presenting with opportunistic infections has been shown to lead to a 50% reduction in AIDS-related mortality compared to patients who were started on ART after completion of OI therapy (late ART).⁹⁶

ART is usually given as follows:

- Two different nucleotide/nucleoside reverse transcriptase inhibitors plus an additional drug. This third drug may be a protease inhibitor, a nonnucleoside reverse transcriptase inhibitor, or an integrase inhibitor.
- CCR5 antagonists and fusion inhibitors are additional alternatives. CCR5 antagonists may be used in treatment naïve patients. Due to toxicities and difficulties in drug administration, fusion inhibitors are usually reserved for ART-experienced patients who have failed therapy and those with multidrug resistance.⁹⁷

The goals of ART therapy are to

- Increase disease-free survival
- Improve immune function
- Reduce HIV transmission risk through decreased viral loads⁹⁷

On initiation of ART, patients may experience immune reconstitution inflammatory syndrome (IRIS) that may be self-limited or have long-term sequela. IRIS occurs when immune function rapidly improves leading to systemic or local inflammatory reactions and a paradoxical worsening of the infectious process.⁹⁸

HIV-positive patients may also need to be screened for certain infections and administered antimicrobials as primary prophylaxis, suppressive therapy, or preemptive therapy if their immune function declines.

Education is key in preventing transmission of HIV. Regardless of HIV status, all patients should be educated on how to protect themselves and others from infection with HIV. Patients at high risk for contracting HIV may consider preexposure prophylaxis (PrEP).⁹⁹ PrEP has been shown to reduce the risk of HIV infection by 92% in high-risk patients.¹⁰⁰ Individuals that may have been recently exposed to HIV, postexposure prophylaxis (PEP) may be started within 72 hours.¹⁰¹

CONCLUSIONS

Most cutaneous viral diseases are self-limited in immunocompetent individuals. Due to the growing number of immunocompromised patients (whether because of HIV/AIDS or iatrogenic causes), life-threatening manifestations of these viral diseases are increasingly common. Although many of these diseases are classically seen in developing countries, air travel and the global economy have brought these infections to the attention of physicians and patients in developed nations as well. Doctors and health-care workers must be careful not to overlook the potential for life-threatening complications of viral skin diseases. Vaccination when available is usually the best strategy for prevention of illness. On infection, prompt treatment is necessary to prevent avoidable morbidity and mortality.

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Life-threatening cutaneous fungal and parasitic diseases

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Cutaneous fungal and parasitic diseases are frequent and usually do not threaten the physical integrity of the patient. There are, however, some that may acquire a severe clinical picture and may even cause death. Some of the most important and/or dangerous of these life-threatening cutaneous fungal (as systemic candidosis, paracoccidioidomycosis, sporotrichosis, zygomycosis, and histoplasmosis) and parasitic diseases (Chagas disease, schistosomiasis, amebiasis, and leishmaniasis) are discussed in this chapter.

FUNGAL INFECTIONS

Systemic Candidosis

First observed by Bernard von Langenbeck (1810–1887) in 1839, the genus *Candida* suffered several taxonomic modifications until its present classification. It presents about 200 species of fungi and shelters the most important yeasts that infect mankind. Many species are opportunistic pathogens; however, the majority do not infect humans.¹ Only a few *Candida* species are colonizers of a human host like *Candida albicans*, *Candida glabrata*, *Candida dubliniensis*, and *Candida parapsilosis*. These species can cause infections that range from superficial to life-threatening disseminated candidosis.²

Although the last decades have observed an increase of infections by the non-*albicans* *Candida* species (such as *C. tropicalis*, *C. glabra*, *C. krusei*, *C. dubliniensis*, and *C. parapsilosis*), *C. albicans* remains the dimorphic yeast responsible for 70%–90% of all infections of this type.^{3,4} It is frequently found as a saprophyte of humans, colonizing the mucosa of the digestive system, and by contiguity, the vaginal mucosa of the majority of mammals.

The term “candidiasis” or “candidosis” (more frequent in Canadian and UK literature) has a generic connotation and encompasses a wide spectrum of clinical manifestations. Invasive candidosis embraces both candidemia and deep-seated tissue candidosis. Candidemia is the most common type of the disease. Hematogenous dissemination or direct inoculation of *Candida* species to a sterile site, such as the peritoneal cavity, causes deep-seated candidosis.⁵

Factors related to the host's immunity, mainly the cell immunity, and characteristics of the microorganism's virulence will determine the spectrum of the disease, which varies from superficial infection of the mucous membranes and skin, to visceral and systemic infections.^{1,4} Neutrophils in innate immunity and CD4 T cells in acquired immunity have a major role in host defense immune response. In vivo studies have revealed excessive IFN γ released from *Candida* and bacterial coinfection that is a critical factor in worsening candidal infection.⁶

Neutropenia, hematologic neoplasias, cancers in solid organs, transplants, and other situations of immunosuppression

are the main substrata for installation of systemic candidosis. Additional aggravating factors to those scenarios are extensive hospital internments, prolonged use of broad-spectrum antimicrobials, hemodialysis, multiple gastrointestinal (GI) procedures, parenteral feeding, and medium- to long-term intravascular catheters.^{4,7,8}

Systemic candidosis is a severe infection, associated with great mortality (approximately 40%–60%) caused mainly by difficulties in its diagnosis, leading to a delay in its recognition. The clinical manifestations are unspecific, and tools for diagnosis are not sensitive enough.^{1,4,9}

The most relevant clinical finding is persistent fever, despite the use of appropriate antimicrobials for the supposed bacterial picture. The remaining manifestations are inherent to the organs affected and to septic syndrome.

Dermatologic lesions affect approximately 10%–13% of patients. Despite *C. albicans* ruling absolute as the cause of systemic disease, *C. tropicalis* is isolated with greater frequency in cases of systemic candidosis with dermatologic manifestations. It is speculated that a greater tropism by cutaneous tissue occurs in the latter.^{10,11}

Newborns present more frequent dermatologic alterations when compared to adults with systemic candidosis.

A 35.8% rate of cutaneous manifestations associated with systemic candidosis has been observed,¹⁰ where 52.6% of the patients with dermatologic manifestations had the onset of dermatitis concurrently with fever and, of these, four patients (40%) presented with a triad of fever, cutaneous eruption, and myalgia.

The cutaneous lesions are varied and multiple: macules, nodules, and erythematous plaques, some purple, with a central lighter hue, affecting especially the trunk and extremities. In some cases, numerous vesicles can mimic herpes zoster. Also, worthy of mention are reports of cellulite lesions and gangrenous ecthyma-like lesions.

The purple lesions have been attributed to the frequent thrombocytopenia found in these patients.^{10,12,13}

Systemic candidosis is a disease of difficult diagnosis. Within some clinical coherence, biopsies of suspect cutaneous lesions and affected organs may suggest the diagnosis; however, the usual stains and immunofluorescence methods may fail in identifying the species.

A biopsy may help to identify spores and/or hypha, mainly in the upper portion of the dermis, surrounding small vessels with varied degrees of vascular damage from dilations, thrombus, red cell extravasation, and even vasculitis.¹⁰

The gold standard is a blood culture, but cultures from other suspected sites can help in the diagnosis (Figures 13.1 and 13.2). The lack of sensitivity (only 50% of the affected patients) and a delay in identifying the agent (approximately



Figure 13.1 *Candida albicans*—culture. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)

1 week) make the method unacceptable for a basis to begin therapy; furthermore, the method has little capacity to identify the species of *Candida*, crucial for an appropriate treatment, because some species are naturally less sensitive or resistant to commonly employed systemic antifungals (Table 13.1).¹⁴

The detection of immunologic and molecular markers, like β -D-glucan and *Candida mannan*, are currently an important tool to make an early diagnosis of invasive candidosis and



Figure 13.2 *Candida albicans*—germ tubes. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)

to monitor the response to therapy. The β -D-glucan is a panfungal marker that, when negative on at least two occasions, has a high negative predictive value. The *Candida mannan*, a genus-specific marker, has sensitivity of ~70% before blood cultures become positive.¹⁵

New methods for biomolecular identification with amplification of deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) represent an indirect detection. Such systems are called “real-time” PCRs (TaqMan system and LightCycler system) and promise immediate results, with optimal sensitivity and specificity. A commercial real-time PCR assay, such as SeptiFast, permits the detection of five major clinically important *Candida* spp. in blood specimens within 6 hours.^{15,16}

The global shift in favor of non-*albicans* *Candida* species shows the emerging resistance to antifungal drugs. The fast and adequate institution of antifungal therapy is necessary for reducing mortality rates.

When possible, treatment should be directed toward the predisposing underlying factors, such as the removal of deep vein accesses.

The choice of agent will depend on (1) the patient’s state (hemodynamically stable, sepsis/shock, predisposing factors to renal inadequacy, etc.); (2) use of previous antifungal medication before the current picture; and (3) isolation of specific microorganisms with known resistance to certain agents (Table 13.2).

For decades, amphotericin B deoxycholate, a polyenic antibiotic of broad-spectrum fungicide action, was used as a treatment of choice for invasive candidosis. Unfortunately, that drug is ill-tolerated, presenting immediate adverse reactions (related to the speed of its infusion; fever, shivers, hypoxemia, and hypotension) and late effects (nephrotoxicity; reduction of glomerular filtration rate and depletion of potassium, magnesium, and bicarbonate).

Two lipid-based formulations were created and are generally available to minimize undesired effects from amphotericin B deoxycholate, mainly nephrotoxicity. Amphotericin lipid complex and liposomal amphotericin possess the same spectrum of activity but daily dosing regimens differ for each agent.^{4,16–19}

With the emergence of triazolic compounds (fluconazole and itraconazole), fluconazole became the most employed medication in the treatment of nonneutropenic and hemodynamically stable patients. It presents a wide action spectrum and good bioavailability; however, *C. krusei* and *C. glabrata* present, respectively, resistance and low sensitivity to fluconazole. The azolic compounds, acting on enzymes of the cytochrome P450 system, interact with several drugs.^{7,20–23}

Already available in intravenous (IV) formulations, itraconazole has variable bioavailability and low serum concentration when compared to other tissues (liver, lungs, and bones) and has a higher interaction with other medications.^{17,18,20}

The second generation of triazolic compounds, such as voriconazole, posaconazole, and ravuconazole, is in advanced study phases. They present an expanded spectrum with smaller risks of interactions with several drugs. Voriconazole and posaconazole are available in venous and oral formulations and comparative studies are showing promising results. Isavuconazole, the latest second-generation triazole antifungal to receive U.S. Food and Drug Administration approval, is administered as the prodrug isavuconazonium. Approved for the treatment of both invasive aspergillosis and invasive mucormycosis, and currently under investigation for

Table 13.1 Susceptibility of *Candida* Species

<i>Candida</i> spp.	Amphotericin B	Fluconazole	Itraconazole	Voriconazole	Caspofungin
<i>C. albicans</i>	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S ^a
<i>C. glabrata</i>	S to I	S-DD to R	S-DD to R	S to I	S
<i>C. krusei</i>	S to I	R	S-DD to R	S	S
<i>C. lusitanae</i>	S to R	S	S	S	S

Source: Data adapted from Flückiger U et al. *Swiss Med Wkly* 2006;136:447–463.

Note: Interpretation based on the use of the National Committee for Clinical Laboratory Standards (CLSI) M27-A methodology. S, susceptible; S-DD, susceptible-dose dependent; I, intermediate; R, resistant.

^a MIC90 (the minimum inhibitory concentration required to inhibit the growth of 90% of organisms) is higher than in other *Candida* species, but clinical significance is unknown (breakpoints not yet defined).

candidemia and invasive candidosis, isavuconazole will probably have therapeutic advantages over its predecessors, because it has an activity reminiscent of the polyene amphotericin B and has been less toxic than voriconazole. Isavuconazole has activity against a number of clinically important yeasts and molds, including *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans*, and *Trichosporon* spp. and variable activity against the Mucorales.^{4,17–22}

The echinocandins (caspofungin, micafungin, and anidulafungin), a class of antifungals with parenteral action, have fungicidal action on different species of *Candida*, including samples resistant to fluconazole and amphotericin B. Different from the remaining antifungals, the echinocandins act on the fungal cell wall. Despite the fact that these agents are only available

as parental formulations, the echinocandins are currently the initial therapy for most adult patients with candidemia. Their exceptional patient tolerance, excellent efficacy, few drug interactions, and concerns about fluconazole resistance make them the first choice of treatment.^{16–18,20}

Investigations encompassing combinations of antifungal agents are scarce and, in certain cases, disappointing. In vivo studies showed antagonism between the simultaneous use of amphotericin B and azoles. The classic association between amphotericin B deoxycholate and 5-fluorocytosin did not show a clear advantage as in the cases of cryptococcosis in immunodepressed patients. In contrast, the combination of caspofungin and meropenem, an ultra-broad-spectrum antibiotic in hospital use, showed a significant superiority to monotherapy.^{4,23}

Table 13.2 Empirical Therapy for *Candida* Bloodstream Infections

Setting	First choice	Alternatives
Nonneutropenic patient and no previous exposure to azoles	Caspo 70 mg loading, then 50 mg/d; Mica 10 mg/d or Anid 200 mg loading, then 100 mg/d	Flu 800 mg/d loading, then 400 mg/d Amphotericin B deoxycholate 1 mg/kg/d IV Or Caspo 70 mg IV (first dose), then 50 mg/d IV Or Voriconazole 6 mg/kg IV q12h on day 1, then 4 mg/kg q12h IV
Nonneutropenic patient and previous exposure to azoles	Amphotericin B deoxycholate 1 mg/kg/d IV or Caspo 70 mg IV (first dose) then 50 mg/d IV	Liposomal Amphotericin B (AmBisome®) 3 mg/kg/d IV
Neutropenic patient	Caspo 70 mg loading, then 50 mg/d; Mica 10 mg/d or Anid 200 mg loading, then 100 mg/d	Liposomal Amphotericin B (AmBisome®) 3 mg/kg/d IV
Severe sepsis or septic shock	Liposomal Amphotericin B 3–5 mg/kg/d; Caspo 70 mg IV (first dose) then 50 mg/d IV ^{a,b} ; Mica 10 mg/d or Anid 200 mg loading, then 100 mg/d	Liposomal Amphotericin B (AmBisome®) 3 mg/kg/d IV Flu 6 mg/kg/d or Voriconazole 6 mg/kg IV q12h on day 1, then 4 mg/kg q12h IV ^{a,b} if no previous azole exposure

Source: Data adapted from Fidel PL Jr. *Oral Dis* 2002;8(suppl 2):69–75; McCarty TP, Pappas PG. *Infect Dis Clin North Am* 2016;30(1):103–124.

Note: According to susceptibility testing. Some experts would add voriconazole to the list of first choice agents for the treatment of *C. glabrata* infections.

^a Few clinical data are available on the use of azoles and echinocandins in neutropenic patients with documented invasive candidosis. In vitro, azoles are fungistatic; echinocandins are fungicidal. In some experimental models (e.g., *Candida* endocarditis, disseminated candidosis in neutropenic animals), azoles are less efficacious than amphotericin B or echinocandins.

^b Amphotericin B deoxycholate is not recommended in critically ill patients with severe sepsis/septic shock: risk of acute nephrotoxicity or of underdosing due to infusion-related toxicity. Caspofungin (Cancidas®) is first choice or alternative, respectively, in this setting.

Paracoccidioidomycosis

Paracoccidioidomycosis was first described in Brazil by Adolfo Lutz (1855–1940), in 1908, and, later, investigated by Afonso Splendore (1855–1940) and Floriano Almeida (1898–1977), in 1912 and 1930, respectively, both with relevant contributions. Lutz-Splendore-Almeida disease and South American blastomycosis are less common names for paracoccidioidomycosis, a term acknowledged by the United Nations since 1971.^{24–26}

Paracoccidioidomycosis is a deep mycosis, the isolated agent of which is the dimorph fungus *Paracoccidioides brasiliensis*, the causative agent of the granulomatous process, predominantly chronic, and implicated on rare occasions in acute and subacute diseases. It is characterized by polymorphism of the lesions and can affect virtually any organ, especially the lymph nodes, lungs, nasal mucosa, and gastrointestinal (GI) tract, besides suprarenal glands and the central nervous system (CNS).²⁵

This polymorphism could be explained with a new discovery from gene sequencing crop samples from Brazil, Venezuela, and Colombia, in which they proposed the existence of three possible new species. In 2009, a fourth species showed a clear difference in morphology and sequencing to the others, published with the suggested name of *P. lutzii* in tribute to Adolfo Lutz.^{27,28}

The geographic distribution of the fungus is directly related to the climate, being found predominantly in tropical and subtropical regions with acid soils. Molecular methods employed in *Paracoccidioides* genus study have promoted significant advances in the knowledge of their ecology: for example the detection of *P. brasiliensis* in different animal species besides the previously described *Dasypus* (armadillo nine bands), like in *D. septemcinctus* (armadillo seven bands), *Procyon cancrivorus* (raccoon), *Cavia aperea* (cavy), *Sphiggurus spinosus* (hedgehog), *Galictis vittata* (ferret), and *Eira barbara* (irara).²⁹

It is an endemic disease in Latin America, with its greatest incidence in South American countries, mainly Brazil, Venezuela, Colombia, Ecuador, and Argentina, without reports of autochthonous cases either in Chile or in the Antilles. There are few cases of the disease in Central America, with predominance in Mexico.

The infection happens in general in the first two decades of life; however, it can remain latent for many years until generating the disease.

Incidence before age 12 is similar in both sexes, with greater risk for the acute and subacute forms of paracoccidioidomycosis. After age 12, there is greater predominance in men (young or middle-aged men, and men who work in rural areas [who are at greater risk of developing the disease in the chronic form]).

The extremely low percentage of women affected during childbearing age can be explained by the assumed inhibition of β -estradiol by the transformation of the mycelia into hyphae, infecting forms of *P. brasiliensis*, after finding receivers of that hormone in the cytoplasm of the fungus.

The greatest risk factor for infection is represented by activities involving handling of polluted soil. Tabagism and alcoholism are frequently associated with the disease.

Different than other systemic mycoses, paracoccidioidomycosis is rarely related to immunodepressive diseases. There have been reports of this mycosis in patients with acquired immune deficiency syndrome (AIDS), neoplasias, and (more rarely) transplants.

The most important infection modality is through the respiratory tract, by inhalation of the spores of the fungus, although there is a report of the disease by direct cutaneous and mucosal inoculation. Starting from the penetration site, the fungus can multiply and disperse into neighboring tissues, reaching the regional lymph nodes or disseminating hematogenically.

Varied clinical forms can be observed in paracoccidioidomycosis, from located benign to disseminated and progressive disease, often with a fatal outcome. Genetic, hormonal, nutritional, and immunologic factors are involved in the development of the infection and its clinical manifestations.²⁵

The classification proposed by the consensus on paracoccidioidomycosis of 2006, developed by the Brazilian Society of Tropical Medicine and adapted at the International Colloquium on Paracoccidioidomycosis (held in February 1986), is shown in Table 13.3.³⁰

After penetration of *P. brasiliensis* into the host, a paracoccidioidomycosis infection results that may resolve spontaneously, progress to a disease, or remain latent, according to the patient's immunity. The main types of paracoccidioidomycosis disease are the acute/subacute forms (juvenile type) and the chronic type. The acute/subacute form is responsible for approximately 5% of the cases of paracoccidioidomycosis, prevailing in children and teenagers of both sexes, presenting rapid evolution. We highlight occurrence of lymph node involvement, hepatosplenomegaly, intraabdominal masses, jaundice, ascites, osteoarticular and cutaneous lesions (approximately 50% of the cases), in addition to rare lung involvement (<5% of the cases).

The chronic form prevails in 90% of the cases of the disease, affecting adults older than 20 years, and can be divided into unifocal or multifocal, according to the number of organs or systems affected, in direct relation to the degree of cellular and humoral immunity.

The oral cavity involvement (Figure 13.3) is predominantly caused by contamination from lung secretions, although a direct inoculation of the fungus can also occur.

The most affected sites are lower lip, mucous membrane, and sublingual area. The lesions can extend to the pharynx, tonsils, and larynx. The typical presentation includes erythematous ulcerated lesions, with granulomatous bases, intermixed with hemorrhagic spots, known as moriform stomatitis of Aguiar-Pupo (Figure 13.4).

The characteristic cutaneous lesions are ulcers or vegetations, but crusted papules, erythematous plates, and nodules may be present. They are located more frequently in the central areas of the face, extremities, and trunk. Cervical lymph node

Table 13.3 Classification of the Clinical Forms of Paracoccidioidomycosis

Paracoccidioidomycosis disease
Acute/subacute form (juvenile type)
Chronic form (adult type)
Unifocal
Multifocal
Residual form or sequel

Source: Data adapted from Shikanai-Yasuda MA et al. *Rev Soc Bras Med Trop* 2006;39:297–310.



Figure 13.3 Paracoccidioidomycosis—oral lesion.



Figure 13.4 Paracoccidioidomycosis—stomatitis of Aguiar-Pupo.

involvement (Figure 13.5) may become suppurative, resembling scrofuloderma.

Visceral involvement is varied but always present. Lungs (Figure 13.6), adrenals, liver, spleen, GI tract, genitourinary tract, CNS, and bones can also be affected.

The residual form or sequela is observed in advanced stages of the disease, where the chronic inflammatory process generates fibrosis and functional restrictions of the affected organs, with lung fibrosis most often.

In view of a clinical and epidemiologic suspicion of paracoccidioidomycosis, methods for isolation and identification of the fungus are required, in addition to serologic techniques that help in the diagnosis and follow-up.²⁶

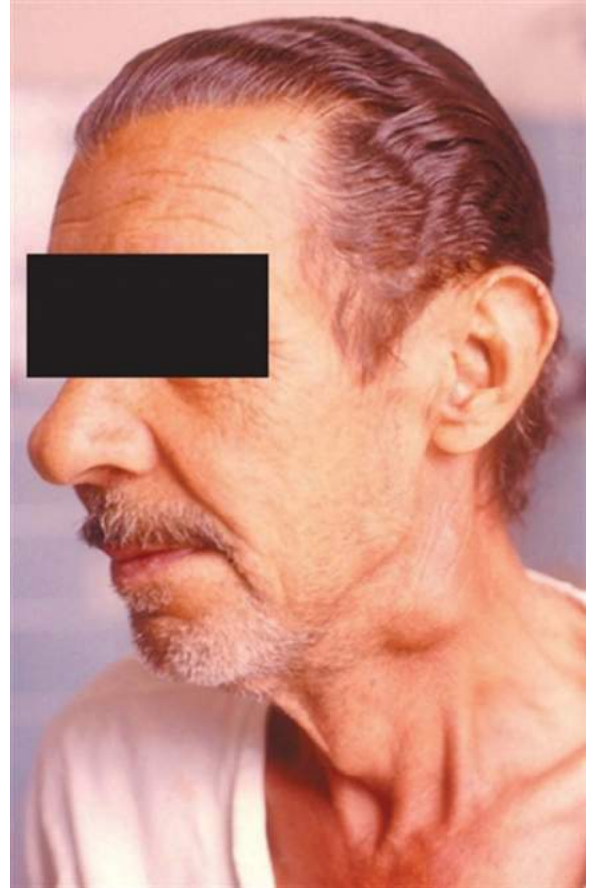


Figure 13.5 Paracoccidioidomycosis—lymph-node enlargement.



Figure 13.6 Paracoccidioidomycosis—x-ray showing lung involvement.

The direct mycologic examination of fresh or Giemsa-stained material shows rounded cells, of double contour, well refringent, varying from 5 to 25 μ m in diameter (Figure 13.7).

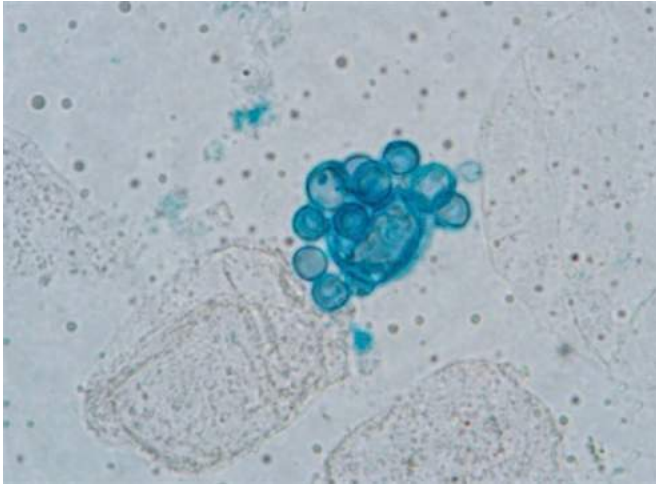


Figure 13.7 *Paracoccidioides brasiliensis*—direct examination of cutaneous biopsy in potassium hydroxide (KOH) and Parker ink. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)

A typical finding is multiple gemulation in the form of a rudder wheel, with multiple gemulation around the fungus.^{25,31}

Cultures are made on Sabouraud or blood agar, with an approximate 20-day duration,³⁰ and they are different if the culture is maintained at 37°C or 25°C (Figure 13.8).

Histopathologic study may reveal a granulomatous pattern, rich in giant and epithelioid cells, some containing different amounts of fungi. The finding of a parasitic element with double walls with simple or multiple gemulation is a positive diagnosis. *P. brasiliensis* can be visualized by hematoxylin and eosin (H&E) stain, but special colorations are required for fungi; periodic acid-Schiff (PAS) and Gomori methenamine–silver (GMS) stains are required, when the amount of parasites is low.

Currently, several serologic techniques for identification of antigens of *P. brasiliensis*, mainly gp43 and gp70, are available from reference services. Double immunodiffusion, counterimmunoelectrophoresis, indirect immunofluorescence, ELISA, and immunoblot are examples that, besides aiding in the diagnosis, present relevant roles in the segment, with important information on the prognosis and activity of the disease.

The titer of specific anti-*P. brasiliensis* antibody is correlated with the severity in the clinical forms, being higher in the acute/subacute forms of the disease. Cases of false-negative serologies can be justified for located forms of the disease, immunodepressed hosts, or AIDS patients. False-positive results are found in patients with histoplasmosis and aspergillosis.³⁰

For its simplicity, acceptable cost, and good sensitivity and specificity, double immunodiffusion has been considered the main technique for diagnosis of paracoccidioidomycosis by consensus of the Brazilian Society of Tropical Medicine.

Other more complex tests are subject to clinical suspicion or initial alterations that predict the involvement of CNS, lung, GI, osteoarticular, or adrenal dysfunction.

The treatment of paracoccidioidomycosis should obligatorily encompass support measures for clinical complications, associated with local and systemic involvement of the mycosis, in addition to specific antifungal therapeutics. Most of

the available systemic antifungal drugs are active against *P. brasiliensis*, such as amphotericin B, sulfamides (sulfadiazine and sulfamethoxazole/trimethoprim), terbinafine, and azolic antifungals, (ketoconazole, fluconazole, itraconazole, and voriconazole).

In mild-to-moderate cases, itraconazole is the option of choice. For its low cost and availability at the public health services, the association of sulfamethoxazole/trimethoprim is widely used in Brazil. Terbinafine has in vitro activity against *P. brasiliensis*, similar to itraconazole, and has been used successfully in the treatment of disseminated disease, in a dosage of 500 mg/day, with a 2-year follow-up.^{26,32} In patients with severe forms of the disease, amphotericin B or IV sulfamethoxazole/trimethoprim is used. In pregnant women, amphotericin B is recommended; in patients with kidney failure, itraconazole or other azole derivative; in patients with liver disease, the best treatment is amphotericin B; and in children, sulfonamides or itraconazole are more practical.³³

IV fluconazole can be considered (400–800 mg/day for 1 month) for cases of neuroparacoccidioidomycosis due to its good penetration into the CNS.²¹ Voriconazole, a second-generation triazolic compound available in oral and IV formulations, is an alternative therapeutic option of great potential.

Treatment is long, related to the severity of the disease as well as to the type of drug employed and should be maintained



Figure 13.8 *Paracoccidioides brasiliensis*—cultures at 37°C and 25°C showing dimorphism. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)

until reaching cure, based on clinical, mycologic, radiologic, and serologic parameters. Clinical cure is defined as resolution of the signs and symptoms of the disease, healing of the integumentary lesions, and regression of adenopathy with recovery of body weight. The demonstration of the agent's elimination or its nonviability represents a mycologic cure. Stabilization of the radiologic findings and regression, being slow for the lung, predicts a radiologic cure.³⁴ Serologic cure occurs when double immunodiffusion shows negative titers or stabilization of the values less than or equal to 1:2 observed in two samples collected in a 6 month interval after the period of specific treatment.³⁰

Every patient presents a potential risk of a late reactivation; for this reason, after observing the criteria for cure and after treatment interruption, patients should be followed semi-annually, at least for the first year with clinical and serologic tests, if necessary.^{25,30}

Vaccines containing antigen gp43 DNA have demonstrated capability to generate protective immunity against *P. brasiliensis* and to be a potential weapon in the prevention of future cases.^{35,36}

Visceral and Disseminated Sporotrichosis

The first case of sporotrichosis was reported in 1896 by Benjamin Schenck (1873–1920), who was at that time a medical student. He isolated the suspect organism and forwarded it to Erwin Smith, a mycology teacher, who concluded that it belonged to the *Sporotrichum* genus. Later, in 1900, Hekton and Perkins classified the pathogenic fungus as *Sporothrix schenckii*.^{37,38}

Although it is found worldwide, *S. schenckii* is more prevalent in the tropics and in hot areas of temperate regions. This dimorphic fungus is present in decaying vegetation, sphagnum moss, and soil. Contamination often occurs by cutaneous inoculation of the organism, preceded by local trauma.

Another less common mode of contamination, but related to more severe forms of the disease, is through inhalation of fungal conidia, generating primary lung lesions (diffuse fibrosis, abscesses, and lymph-node enlargement) with posterior hematogenous dissemination.³⁹

Farmers, gardeners, horticulturists, and forest workers are most susceptible to the infection. Sporotrichosis can be transmitted by scratches and bites from digging animals that carry the microorganism in their paws and teeth.⁴⁰ An epidemic of sporotrichosis in cats has occurred with a consequent increase of reports of infections transmitted by those sick animals.^{41,42}

Sporotrichosis is a subcutaneous mycoses and is generally restricted to the skin and subcutaneous tissue. Osteoarticular, visceral, and disseminated lesions are uncommon and present greater morbidity. Osteoarticular manifestations are the most frequent among the cases of extracutaneous disease. The immune conditions of the host and the contamination route are the factors of greater relevance for the severity of the disease. The possibility of virulence factors associated with different genotypes of *S. schenckii* may contribute to the distinct clinical forms of sporotrichosis.⁴³

Patients with AIDS, chronic alcoholics, and malnourished, transplanted, or immunodepressed patients in general are most susceptible to the disseminated forms (Figures 13.9 and 13.10). Patients with AIDS present a special risk for developing more severe forms. The diagnosis of cutaneous or



Figure 13.9 Sporotrichosis—cutaneous lesion patient with lymphoma. (Courtesy of Nurimar Fernandes, MD, PhD, and Hugo Alves, MD, Rio de Janeiro, RJ, Brazil.)

lymphocutaneous sporotrichosis in an AIDS patient justifies the search for disseminated lesions in other organs, including the CNS. Disseminated lesions may result in arthritis, mastitis, meningitis or multiple cerebral abscesses, orchitis, pyelonephritis, and bone infections.

Cutaneous manifestations can arise in the process of disease dissemination and are characterized by painful nodules that evolve into ulcers. Papules, pustules, and other elementary lesions are occasionally observed.³⁸



Figure 13.10 Sporotrichosis—cutaneous lesion with multiple myeloma.

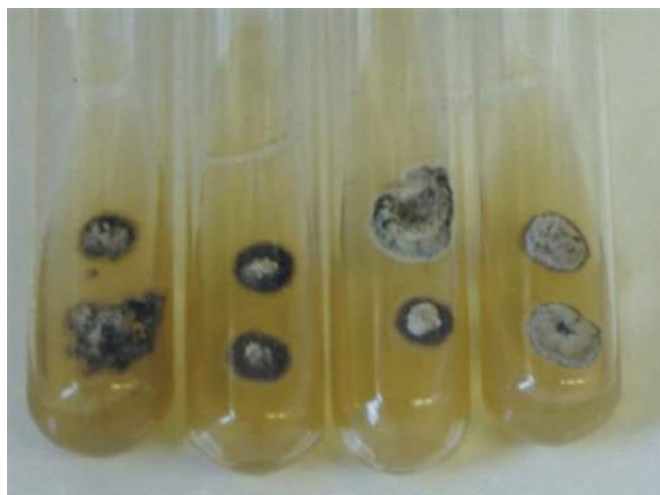


Figure 13.11 *Sporothrix schenckii*—cultures at 25°C. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)

Due to the few reported cases and similarity of their clinical manifestations to other more common diseases such as tuberculosis, paracoccidioidomycosis, cryptococcosis, and sarcoidosis, the diagnosis of visceral sporotrichosis is frequently delayed.

Culture is the gold standard for diagnosis. Aspirates, scrapings, and biopsies of suspect lesions, cutaneous or not, can serve as substrata. Cultures of synovial liquid and/or liquor can be adequately accomplished. The culture is initially white, acquiring a darker color later (Figure 13.11). In 89% of cases, isolation of *S. schenckii* is obtained in approximately 8 days. The growth of the fungus can occur later, sometimes taking up to 4 weeks. Microscopy of the culture shows conidia in a flower head arrangement (Figure 13.12). Direct examination does not help due to the very small amount of fungal cells, commonly present in the examined materials.

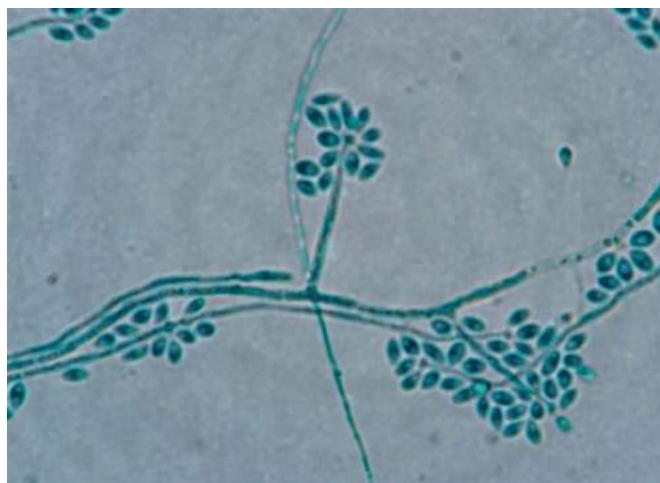


Figure 13.12 Potato-dextrose agar growth of *Sporothrix schenckii* (PDA) A smear stained with methylene blue. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)

A histopathologic study can disclose an unspecific granulomatous reaction with pseudoepitheliomatous hyperplasia and intraepidermal abscesses. Rarely, in PAS or silver stain, oval and cigar-shaped organisms are observed, with diameters of 3–5 μ m inside the granuloma. The asteroid bodies are observed in 40% of the rare cases in which these microorganisms are found. They can be seen in other granulomatous reactions; however, extracellular structures made of spiculae of eosinophilic material involved by a center containing yeasts (Splendore-Hoeppli phenomenon) are specific of the asteroid bodies in sporotrichosis.^{38,39,44}

The test of late reaction with sporotrichin is of little use in cases of visceral infections or in dealing with patients with inadequate immune response, in addition to the incapacity of differentiating previous exposure. Serologic examinations did not prove useful in the diagnosis of sporotrichosis and are not widely available.

The cutaneous and cutaneolymphatic lesions are responsive to the therapy using a saturated solution of potassium iodide (SSKI), triazoles (especially itraconazole), terbinafine, and even local heat application.⁴⁵

With the exception of osteoarticular lesions, having a reasonable response to itraconazole, the remaining extracutaneous infections (visceral and disseminated) fail to respond to commonly used medications. Present guidelines for the management of sporotrichosis are summarized in Table 13.4.³⁹

In cases of disseminated or visceral disease, administration of amphotericin B is mandatory, preferably in lipidic formulations. After a favorable response, the parenteral medication can be replaced with itraconazole for a minimum of 12 months. In patients with AIDS, itraconazole can be used indefinitely, as collateral prevention, in a daily dosage of 200 mg. Surgical treatment combined with amphotericin B can be recommended in localized visceral cases, mainly in pulmonary sporotrichosis.

Among the second-generation triazoles, voriconazole shows less antifungal activity against *S. schenckii* than does itraconazole and without indications in cases of sporotrichosis. Posaconazole presents activity against isolated *S. schenckii* samples, but no comparative study has been published.

In a published Mexican study⁴⁶ the production of melanin by *Sporothrix* was demonstrated. This fact might positively influence the discovery of effective therapeutic interventions. Herbicides directed to melanin biosynthesis, such as tricyclazole, are available for agricultural use.³⁹

Zygomycoses

The term “zygomycosis” characterizes any disease caused by fungi of the *Zygomycetes* class and includes two groups of pathogenic microorganisms of medical importance: the order of the *Mucorales* and that of the *Entomophthorales*.⁴⁷ Several species of genera *Rhizopus* (Figures 13.13 and 13.14), *Mucor*, and *Absidia*, may cause the disease.

Mucorales cause an aggressive disease called mucormycosis, which is angioinvasive, rapidly destructive, and in most cases fatal. Although *Entomophthorales*, responsible for entomophthoromycoses, are known for causing mucocutaneous and subcutaneous, painless, and chronic infections, recently a change in the profile of virulence and geographic distribution of these fungi was found that can cause clinical syndromes that are indistinguishable from those caused by the *Mucorales*, making a differentiation between the two orders

Table 13.4 Summary of Recommendations

Lymphocutaneous/Cutaneous	Itr 200 mg/d	Itr 200 mg b.i.d.; or terbinafine 500 mg b.i.d.; or SSKI with increasing doses; or fluconazole 400–800 mg/d; or local hyperthermia ^a
Osteoarticular	Itr 200 mg b.i.d.	Lipid AmB 3–5 mg/kg/d; or deoxycholate AmB 0.7–1 mg/kg/d ^b
Pulmonary	Lipid AmB 3–5 mg/kg/d, then Itr 200 mg b.i.d.; or Itr 200 mg b.i.d.	Deoxycholate AmB 0.7–1 mg/kg/d, then Itr 200 mg b.i.d.; surgical removal ^c
Meningitis	Lipid AmB 5 mg/kg/d, then Itr 200 mg b.i.d.	Deoxycholate AmB 0.7–1 mg/kg/d, then 200 mg b.i.d. ^d
Disseminated	Lipid AmB 3–5 mg/kg/d, then Itr 200 mg b.i.d.	Deoxycholate AmB 0.7–1 mg/kg/d, then 200 mg/b.i.d. ^e
Pregnant women	Lipid AmB 3–5 mg/kg/d or deoxycholate AmB 0.7–1 mg/kg/d for severe disease; local hyperthermia for cutaneous disease	— ^f
Children	Itr 6–10 mg/kg/d (400 mg/d maximum) for mild disease; deoxycholate AmB 0.7–1 mg/kg/d for severe disease	SSKI with increasing doses for mild disease ^g

Source: Data adapted from Kauffman CA et al.; Infectious Diseases Society of America. *Clin Infect Dis* 2007;45:1255–1265.
Note: AmB, amphotericin B; b.i.d., twice per day; Itr, itraconazole; SSKI, saturated solution of potassium iodide.

- ^a Treat for 2–4 weeks after lesions resolve.
- ^b Switch to Itr after favorable response if AmB used. Treat for a total of at least 12 months.
- ^c Treat severe disease with an AmB formulation followed by Itr. Treat less severe disease with Itr. Treat for a total of at least 12 months.
- ^d Length of therapy with AmB is not established, but therapy for at least 4–5 weeks is recommended. Treat for a total of at least 12 months. May require long-term suppression with Itr.
- ^e Therapy with AmB should be continued until the patient shows objective evidence of improvement. Treat for a total of at least 12 months; may require long-term suppression with Itr.
- ^f It is preferable to wait until after delivery to treat non-life-threatening forms of sporotrichosis.
- ^g Treat severe disease with an AmB formulation followed by Itr.

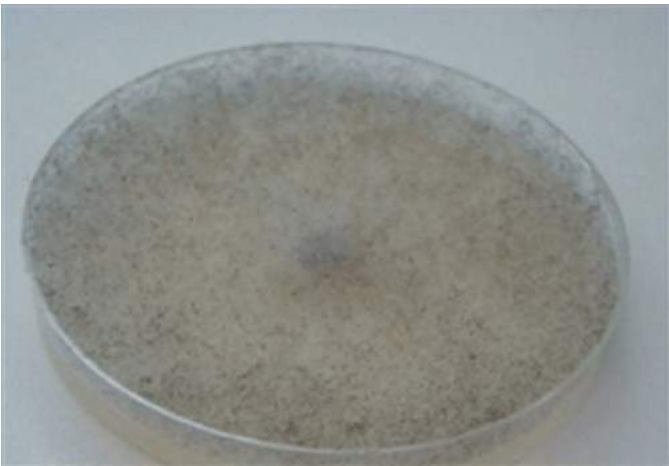


Figure 13.13 *Rhizopus* sp.—culture. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)



Figure 13.14 *Rhizopus* sp.—culture microscopy. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)

impossible, based solely on epidemiologic observation or even at histopathologic examination.⁴⁸
Despite the majority of zygomycosis cases being caused by *Mucorales*, the term “zygomycosis” is preferable to mucormycosis, by being more encompassing and designating disease, even when the cultures are not available, and identification of the fungus is not made.
Recent studies show that zygomycosis is an emerging non-*Aspergillus* mycosis of relevant significance, in part due to the constant increase of cases of diabetes and growing use of immunosuppressive drugs available from the progress

of modern medicine. Inhalation, ingestion, and cutaneous exposure to microorganisms are the main infection sources, and the predisposing factors are listed in Table 13.5.⁴⁷
Diabetes mellitus with metabolic acidosis is implicated in the most cases (36%–88%), although zygomycosis has been observed in metabolically controlled diabetes patients. The average survival rate in diabetic patients with zygomycosis is approximately 60%. The relative treatment facility of acute complications, compared with the remaining immunocompromising conditions, helps to explain the lower mortality rate in cases of zygomycosis associated with diabetes mellitus.

Table 13.5 Factors Predisposing Patients to Zygomycosis

Diabetes mellitus
Diabetic ketoacidosis
Poorly controlled diabetes mellitus
Chronic metabolic acidosis
Renal failure
Chronic salicylate poisoning
Deferoxamine therapy
Iron overload
Immunosuppression
Neutropenia (due to malignancies or chemotherapy)
Corticosteroid therapy
Organ or hematopoietic cell transplantation
Human immunodeficiency virus infection
Skin or soft tissue breakdown
Burn
Trauma
Surgical wound
Miscellaneous
Intravenous illicit drug use
Neonatal prematurity
Malnourishment
Prolonged use of broad-spectrum antimicrobial agents

Source: Data adapted from Conti Diaz IA. *Mycopathologia* 1989;108:113–116.

Excess of iron (by transfusion or by dyserythropoiesis) in addition to therapy with deferoxamine for treatment of excessive albumin and/or iron in patients in dialysis is an important risk factor for angioinvasive zygomycoses. Seventy-eight percent of patients on dialysis and with zygomycosis were treated with deferoxamine.⁴² The more common presentation of the disease is the disseminated form (44%), followed by the rhinocerebral form (31%).

Zygomycosis, associated with deferoxamine therapy, causes significant mortality, approximately 80%,⁴⁷ and in immunosuppressed patients it is frequently fatal (68%–100%). A prolonged neutropenia represents the greatest risk factor of this group, approximately 15% of all cases of zygomycosis.

Pulmonary disease is the most common presentation in neutropenic patients, with the disseminated form more common in individuals with greater immunosuppression. Systemic steroids are another factor favoring zygomycosis, whether by action of macrophages and neutrophils or by steroid-induced diabetes. Patients with AIDS are known to be at risk; however, the majority of cases of zygomycosis in human

immunodeficiency virus (HIV)-infected persons are also associated with IV drug abuse.⁴⁹

Temporary local trauma and burns can also lead to accidental inoculation of fungus spores, generating cutaneous disease even in immunocompetent hosts. The use of broad-spectrum antibiotics and topical preparations with antibacterial effect in burned patients seems to increase the risk of cutaneous fungal infection significantly, including cutaneous zygomycosis.⁵⁰

Other predisposing factors include abuse of illicit IV drugs, premature birth, malnutrition, sites of IV catheter insertion, and extensive therapy with broad-spectrum antimicrobials. Prolonged use of voriconazole for prophylaxis and treatment of invasive fungal infections may increase the risk for several forms of zygomycosis.^{47,51}

Based on the clinical presentations and involvement sites, zygomycoses can be classified as rhinocerebral, pulmonary, cutaneous, GI, disseminated, and miscellaneous, as involvement of CNS without alteration of the paranasal sinuses, endocarditis, and pyelonephritis.

Primary findings may include edema, pustules, plates, bullae, nodules, ulcerations, gangrene-like ecthyma lesions, necrotizing fasciitis, osteomyelitis, and dissemination of the infection.⁴⁷ Cutaneous manifestations of hematogenous dissemination frequently result in painful erythematous lesions, cellulite-like, with central necrosis and eschar, resulting from the angioinvasive action of the fungus.⁴⁷ There is a certain correlation between the predisposing factor and the clinical site or form of the disease, as can be seen in Table 13.6.

With clinical suspicion, the diagnosis of zygomycosis can be made through histopathologic examination of the supposedly committed tissues, in which characteristic broad, hyaline, ribbon-like, wide-angled branching, pauciseptate irregular fungal hyphae accompanying tissue necrosis and angioinvasion of the fungi are found. The tissue invasion by hyphae is essential for the diagnosis. The samples can be stained routinely by H&E, but fungal elements are better observed with special stains such as the GMS, PAS, or calcofluor white stain. Perineural invasion is seen in 90% of tissues containing such elements for sampling. The inflammatory response may be absent, or there may be neutrophils or granulomas.⁴⁷

Large hyaline, nonseptated or irregularly septated, thick-walled hyphae (coenocytic hyphae) can be observed directly in samples from a bronchoalveolar wash and also from other materials prepared with potassium hydroxide (Figure 13.15). Direct immunofluorescence can be employed with samples prepared for maceration by potassium hydroxide and use of calcofluor white, blank fluor, or UVITEX.

Table 13.6 Relationship between Predisposing Condition and Site of Infection

Predisposing condition	Predominant site of infection (in decreasing order of frequency)
Diabetic ketoacidosis	Rhinocerebral and pulmonary
Iron overload and deferoxamine	Disseminated and rhinocerebral
Neutropenia	Pulmonary and disseminated
Corticosteroids and immunosuppression	Pulmonary, disseminated, or rhinocerebral
Trauma, catheter/injection sites	Cutaneous/subcutaneous
Malnourishment	GI
Prolonged broad-spectrum azole use	Pulmonary, disseminated, GI, or rhinocerebral

Source: Data adapted from Spellberg B, Edwards J Jr., Ibrahim A. *Clin Microbiol Rev* 2005;18:556–569.

Note: GI, gastrointestinal.

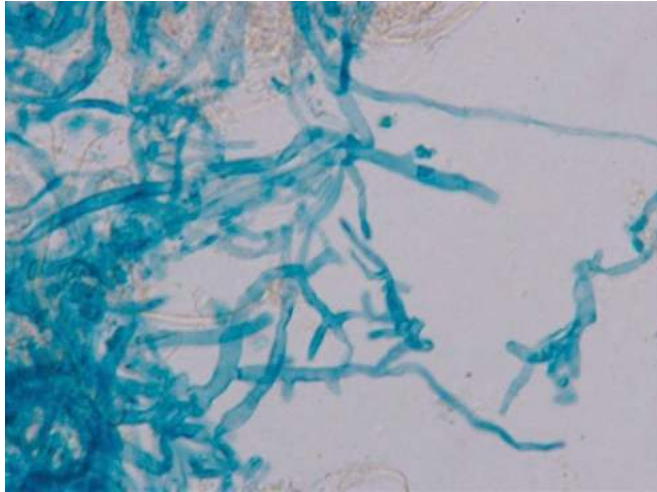


Figure 13.15 Zygomycosis—direct examination—kenocytic hyphae in KOH and Parker ink. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)

The differentiation between zygomycoses (mucormycosis/entomophthoromycosis) can be made by some histopathologic peculiarities: broad fungal hyphae with sparsely found septum surrounded by eosinophilic granular material (Splendore-Hoeppli phenomenon) and peripheral eosinophilia, which are not usually seen in *Mucorales*, favoring the suspicion of *Entomophthorales*.⁴⁷

Hemocultures in all forms of zygomycoses are frequently negative, even when fungal hyphae. The physician should attempt to identify the agent, aiming at better guiding his or her therapy, because the differentiation of *Mucorales*/*Entomophthorales* with other filamentous fungi at histopathologic examination is difficult.

Contamination of clinical samples by *Zygomycetes* is common due to the small size of the sporangiospores, facilitating their airborne dissemination. In any case, isolation of *Mucorales*/*Entomophthorales* from sterile sites or repeatedly positive nonsterile cultures in patients with significant risk factors should be considered highly suspect.

Different techniques of molecular serological examinations are appearing but are not being recommended as routine procedures because of lack of studies and few satisfactory results.

Despite the growing clinical suspicion of the cases of zygomycoses, based on the best knowledge of the predisposing factors, more than half of the mucormycosis diagnoses are obtained postmortem.

The treatment of patients with zygomycosis by *Mucorales* is frustrating; therefore, an early diagnosis should be the objective in patients with high risk, and treatment should be initiated as soon as possible. A multifactor approach should be initiated as early as possible. Treatments include appropriate antifungal therapy, surgical debridement, and correction or resolution of the predisposing factors, such as control of comorbidities and adjuvant therapies for improving the host's immune response.

Despite frequent use of amphotericin B deoxycholate (1–1.5 mg/kg/d), lipidic amphotericin B formulations represent the first line of treatment because they are potentially the

least toxic and have better clinical response than do high doses. Those compounds should be used in initial doses of 5 mg/kg/d, increasing to significant doses and for an extended time, not less than 6–8 weeks.⁵¹

Among the azolic compounds, itraconazole has action in some strains of *Mucorales*; however, it has been implicated as a risk factor for zygomycosis in prolonged use. Of the second-generation imidazoles, voriconazole is not effective in vitro. It has also been frequently implicated in cases of zygomycosis with long-term use after prophylaxis for other systemic fungal infections. Posaconazole and ravuconazole have in vitro action against agents of mucormycosis. Posaconazole as monotherapy or in combination with lipidic formulations of amphotericin B should prove beneficial.⁵¹ Caspofungin and micafungin seem to be ineffective as monotherapy but present a synergic effect when used with amphotericin B.⁵¹

Zygomycosis (mucormycosis) is rapidly progressive, and antifungal therapy alone is inadequate to control the infection. The numerous agents of zygomycosis have a wide spectrum of susceptibility to drugs used, and some can be highly resistant to amphotericin B. Additionally, thrombosis and tissue necrosis resulting from angioinvasion generate an environment with poor penetration by systemic agents into the sites affected by the infection.⁴⁷ Even if the causative agent is susceptible and the drug does penetrate the affected site appropriately, tissue necrosis is not prevented with the death of the microorganism.⁴⁷ Surgical debridement is not only crucial but also highly recommended and should be initiated quickly and repeated several times, which may cause deformities.

Correction of the metabolic disturbances and reversal of the immunosuppression are essential for the treatment of zygomycosis. In patients with diabetic ketoacidosis, hyperglycemia and acidosis should be corrected as soon as possible. Immunosuppressors, especially systemic steroids, should be discontinued, if possible, or at least have their doses significantly reduced.

The main role of iron metabolism in the pathogenesis of zygomycosis suggests the possibility of using iron chelate as therapeutic adjuvant. In contrast to deferoxamine, other oral iron chelates did not allow an iron offer to the microorganism and did not favor the growth of the same in vitro.^{51,52}

Although cytokines are not recommended as routine therapy, granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor as adjuvant therapy have been considered in cases of conventional therapy failure. The use of hyperbaric oxygen therapy finds support in the hypothesis that the high oxygen pressure might improve the capacity of the macrophages to fight the infection.⁵¹

HISTOPLASMOSIS

Histoplasma capsulatum var. *capsulatum* infection is a common infection in areas of the United States and Latin America where it is endemic, but some cases have also been reported from Europe. In the United States, most cases have occurred within the Ohio and Mississippi River valleys (moderate climate, humidity, and soil characteristics). Bird and bat excrement enhances the growth of the organism in soil by accelerating sporulation. Air currents carry the conidia for miles, exposing individuals who were unaware of contact with the contaminated site. Histoplasmosis causes progressive infection in immunocompromised individuals and in persons with underlying chronic lung disease. Certain forms of histoplasmosis



Figure 13.16 Histoplasmosis—lesion on the tongue in a patient with AIDS.

cause life-threatening illnesses and result in considerable morbidity, whereas other manifestations cause either no symptoms or minor self-limited illnesses.⁵³ In some cases of immune depression (Figures 13.16 and 13.17), disseminated histoplasmosis appears in the eyes, oral cavity, larynx, CNS, GI tract, and, more rarely, the sinonasal region.⁵⁴

Laboratory diagnosis is made by direct examination in which, with special staining, small round intracellular fungal structures may be observed (Figure 13.18). The small round forms, similar to *Leishmania*, can also be seen in histopathological preparations. At 25°C, the colonies have a cotton aspect and are a white to beige color, whereas at 37°C they are leveduri-form (Figures 13.19 and 13.20). In microscopy, hyaline, septated, and branched hyphae; thick and spiculated walled, round macroconidia; and oval microconidia are observed (Figure 13.21).

Treatment is indicated only in patients with chronic pulmonary disease and in those with severe forms of acute pulmonary illnesses or in those with the disseminated form of infection with mild to moderately severe manifestations. The drug of choice for the treatment of disseminated histoplasmosis is amphotericin B (0.5–0.7 mg/kg/day for 10 weeks), followed by itraconazole (200 mg three times daily and maintained with 400 mg/day for 12 weeks). In patients with AIDS, the treatment may fail because the absorption is variable, resulting in the inability to achieve therapeutic concentrations in blood.^{55–57}

PARASITIC DISEASES

American Trypanosomiasis or Chagas Disease

Trypanosomiasis is a tropical and mainly rural parasitic disease of blood and various organs. There are two different entities: African, caused by trypanosomes of the *Trypanosoma brucei* group (*T. gambiense* and *T. rhodesiense*), transmitted by tsetse flies, also called sleeping sickness; and Chagas disease, also known as American trypanosomiasis.⁵⁸ Chagas disease, described in 1909 by Carlos Chagas (1879–1934), occurs in rural areas, in wattle and daub houses in tropical zones of the Americas. It is also called *Trypanosomiasis americana* and is caused by *Trypanosoma cruzi*, a parasite of humans and domestic



Figure 13.17 Histoplasmosis—disseminated lesions and herpes infection on the left side of the lip in a patient with AIDS.

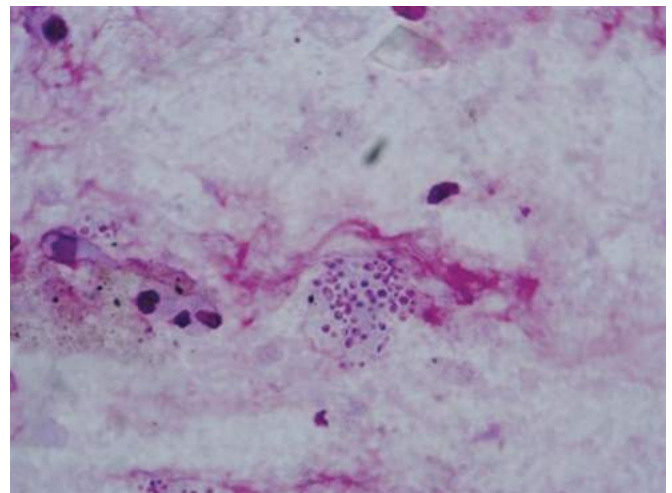


Figure 13.18 *Histoplasma capsulatum*—direct examination—Giemsa stain. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)



Figure 13.19 *Histoplasma capsulatum*—culture at 25°C. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)

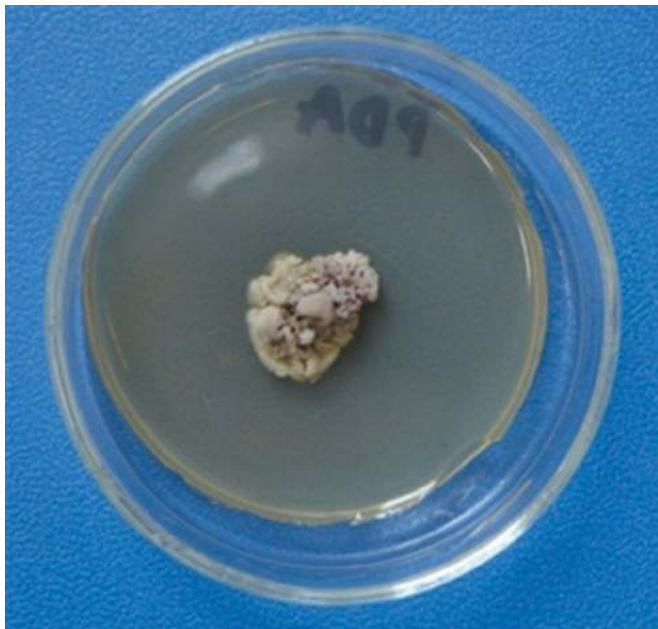


Figure 13.20 *Histoplasma capsulatum*—culture at 37°C. (Courtesy of Mycology Laboratory—HUCFF/UFRJ.)

or wild animals. The transmission is through a sting by the vector animal, the *Triatominae* (“barbeiro”). Age, sex, and race do not influence the incidence of the disease, despite the acute phase being more frequent in children.⁵⁹

Chagas disease is produced by a hemoflagellated protozoan, *Trypanosoma cruzi* (Chagas, 1909) (Figure 13.22), affecting

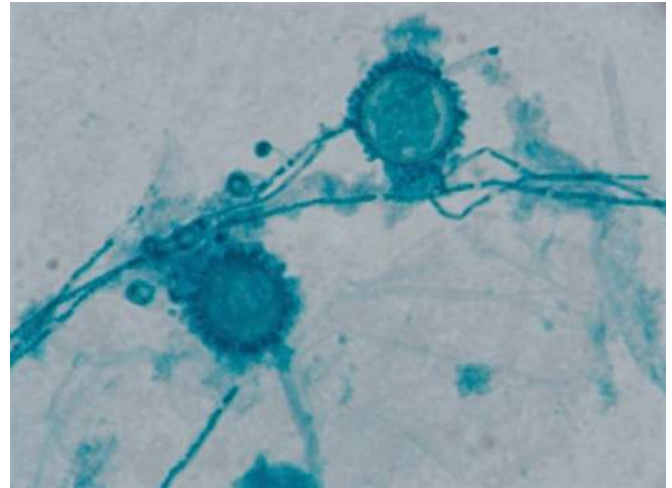


Figure 13.21 *Histoplasma capsulatum*—culture microscopy. (Photo courtesy of Mycology Laboratory—HUCFF/UFRJ.)

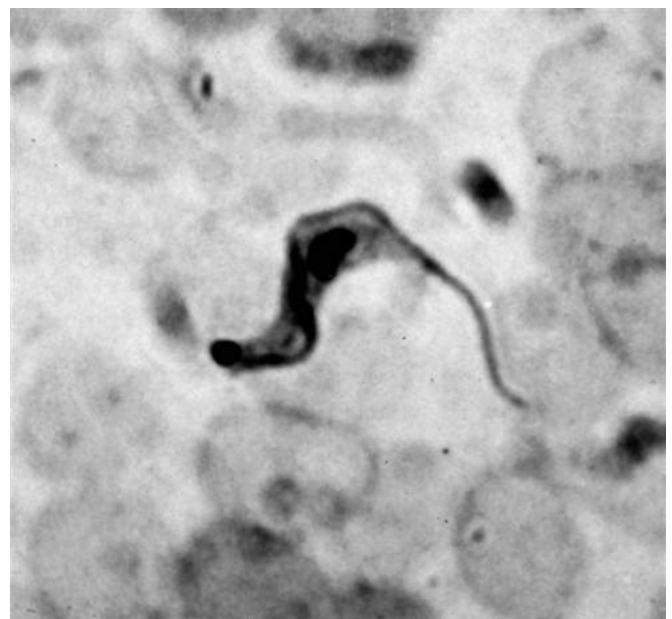


Figure 13.22 *Trypanosoma cruzi*. (Courtesy of Luis Rey, MD, Rio de Janeiro, RJ, Brazil.)

humans and various domestic or wild mammals that act as reservoirs. It is transmitted by bloodsucking invertebrates of the order Hemiptera, genera *Triatoma*, *Panstrongylus*, and *Rhodnius*, called reduviid, assassin, or kissing bugs and “barbeiro” in Brazil (Figure 13.23). Transfusional and congenital infections are also possible, although rare.⁵⁸

Two cycles of circulation of the parasite are known in nature: the wild and the domestic. The wild cycle occurs among marsupials, rodents, monkeys, mice, rabbits, and the triatomid. The domestic cycle results from contamination of animals that live in the vicinity of human dwellings. The trypomastigote



Figure 13.23 Chagas disease—reduviid bug. (Courtesy of Luis Rey, MD, Rio de Janeiro, RJ, Brazil.)

form circulates in the peripheral blood of vertebrates; undergoes transformation in the organism of the vector to the epimastigote form; and multiplies, becoming metacyclic trypomastigotes in the digestive system of the triatomine.⁵⁹ The main species of this arthropod is *Triatoma infestans* (Argentina, Bolivia, Brazil, Chile, Paraguay, Peru, and Uruguay), *Rhodnius prolixus* (Colombia, Guyana, Venezuela, and Central America), and *Panstrongylus megistus* (Brazil). Transmission occurs through the feces of *Triatominae*, which habitually defecate while feeding.^{60–62}

Acute Chagas disease is more frequently seen in children and begins with inflammatory lesions at the inoculation site of the parasite in the skin or conjunctiva, called a Romana sign (Figure 13.24). The inoculation chagoma is a macular or papulonodular lesion, erythematous-violet, hard, and painless, that can ulcerate but tends to regress in 3 weeks. Other signs of disease are satellite lymphadenitis, fever, indisposition, cephalgia, myalgia, hepatosplenomegaly, and maculopapular, morbilliform, or urticariform cutaneous rashes (schizotrypanis).



Figure 13.24 Chagas disease—Romana sign. (Courtesy of João Dias, MD, and Luis Rey, MD, Rio de Janeiro, RJ, Brazil.)

The following phases may present megaesophagus megacolon and affection of the heart, with myocarditis, arrhythmias, and complete blocking.^{58,61,63}

During the acute phase, direct examination of Giemsa-stained blood smears, imprints of skin, or lymph-node biopsy can easily show the parasite.⁵⁸ The search for anti-*T. cruzi* immunoglobulin M antibodies by indirect immunofluorescence and PCR and (in the chronic phase) serological tests with indirect hemagglutination, indirect immunofluorescence, and ELISA are useful.⁵⁵ They can also be demonstrated by blood culture in NNN medium or by animal inoculation.⁵⁸

Xenodiagnosis of Brumpt is also helpful. For this, an uninfected reduviid bug is allowed to bite and feed on the forearm of the suspect patient; 30–60 days later, the insect's feces are examined for the infective form. During the chronic phase, the Machado-Guerreiro complement fixation test using antigens of cultured *T. cruzi* is most useful. ELISA, hemagglutination, indirect immunofluorescence, and PCR can also diagnose the disease.⁵⁸

Available therapeutic agents are unsatisfactory, and treatment does not change the serologic reactions or degradation of cardiac function in chronic phases, despite possibly curing the patient in the acute phase. The two main drugs, benznidazole and nifurtimox, are active against circulating and tissue forms and should be administered for 30–90 days.^{59,63,64}

For patients with stable chronic disease, treatment includes antiarrhythmics and control of the affected systems. Prevention of the disease requires sanitation education and use of insecticides.^{59,64}

Schistosomiasis

Schistosomiasis is one of the most important helminthic infections due to its wide geographic distribution and extensive pathologic effect. It is a systemic disease, caused by human trematodes or flukes. These trematodes affect approximately 200 million people worldwide, mainly in the tropical and subtropical latitudes; sometimes entire communities are affected. Most infected persons experience few, if any, signs and symptoms, and only a small minority will develop significant disease.^{65,66}

Schistosomiasis or bilharziasis is an infection caused by five types of blood flukes of the genus *Schistosoma*. Humans are infected by the cercarial stage of the parasites released from freshwater snails in ponds, canals, lake edges, and streams. Penetration of intact skin occurs rapidly, and the schistosomes migrate into the portal system to mate and then to a part of the venous system to lay eggs. High infection rates persist among both the rural and urban poor. Rural living, poor housing and water supplies, and low educational level are major factors in schistosomiasis occurrence among agricultural populations.⁶⁷

In Brazilian urban areas, prevailing living conditions in shantytowns and labor migrations from and periodic return movements to rural areas were predictive of schistosomiasis. The risk of the establishment of new transmission foci exists in both rural and urban areas, conferred by and affecting poorer people.^{68–70}

In sub-Saharan Africa, there is high prevalence of parasitic worm infections, such as schistosomiasis. The hypothesis of whether a helminth infection increases the susceptibility of the host to acquire de novo infection with an immunodeficiency virus after mucosal exposure, which is the predominant route of HIV transmission in humans, has been tested.⁷¹

The schistosome-infected monkeys have significantly higher levels of initial virus replication and loss of a certain subset of memory T cells, both predictors of a more rapid progression to immune dysfunction. Worm infestations may increase the risk of individuals with viral exposures becoming infected with HIV-1 and also suggest that control programs for schistosomiasis and perhaps other parasitic worm infections may be useful in helping to reduce the spread of HIV/AIDS in developing countries where helminths are endemic.

Contrary to previous reports that indicated no transmission of schistosomiasis at altitudes higher than 1400 m, schistosomiasis transmission can take place at an altitude range of 1487–1682 m above sea level in western Uganda.⁶⁴ Eggs laid in bladder and pelvic and rectal venous plexuses return to the local water supply to complete the cycle through the snail population. Cercarial penetration of the skin may produce an itch eruption, which may be followed by myalgia, headache, and abdominal pain.

Abdominal pain, diarrhea, malabsorption, and (occasionally) intestinal obstruction and rectal prolapse; cirrhosis of the liver associated with portal hypertension, splenomegaly, and esophageal varices; recurrent hematuria and eventually bladder calcification; and obstructive uropathy and renal failure are late manifestations of the disease. Periovaric or schistosomotic granuloma may rarely occur on the skin or vulva (Figure 13.25). Migration of eggs to the lungs may cause massive chronic fibrosis.

Detection of the characteristic ova in the stools, in urine, or on biopsy (Figure 13.26) or with an ELISA are diagnostic.

Treatment involves praziquantel given as a single dose.^{68–70} There are new developments in schistosomiasis diagnosis, including microscopic rapid diagnostic tests for antigen detection and PCR assays.⁷²

Despite many years of implementation of drug therapy programs, this disease continues to spread to new geographic areas. The discovery of a protective vaccine remains the most potentially effective means for the control of this disease. Several vaccine candidates have been studied, including



Figure 13.25 Schistosomiasis—vulval granuloma. (Reproduced with permission from Ramos-e-Silva M, Fernandes NC. Parasitic diseases including tropical. In: Parish LC, Brenner S, Ramos-e-Silva M, editors. *Women's Dermatology: From Infancy to Maturity*. Lancaster (UK): Parthenon; 2001:291–302.)

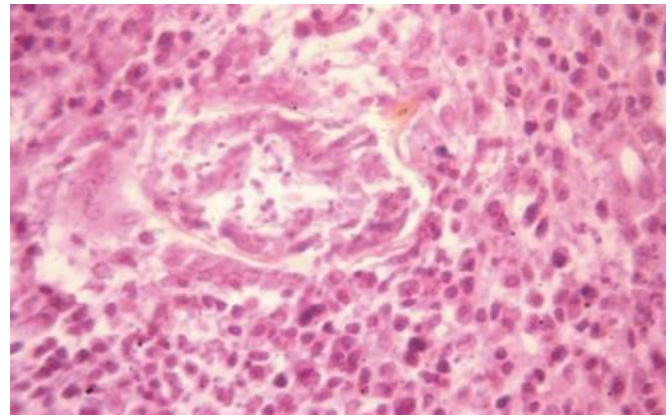


Figure 13.26 Schistosomiasis—biopsy of vulval granuloma showing egg and inflammatory infiltrate. (Reproduced with permission from Ramos-e-Silva M, Fernandes NC. Parasitic diseases including tropical. In: Parish LC, Brenner S, Ramos-e-Silva M, editors. *Women's Dermatology: From Infancy to Maturity*. Lancaster (UK): Parthenon; 2001:291–302.)

tetraspanins (TSP-1/2), which are present on the apical syncytial surface of *S. mansoni*.⁷³ Paramyosin (Pmy), an invertebrate muscle-associated protein, has emerged as a promising vaccine candidate for both *Schistosoma mansoni* and *Schistosoma japonicum*.⁷⁴

Amebiasis

Amebiasis is an intestinal parasitic disease that may affect the skin, especially the perianal and genital areas. It is caused by a common and worldwide intestinal unicellular parasite, *Entamoeba histolytica*, the only human pathogenic species of this genus. The invasive form found in the tissues is a 20–40 µm elongated cell, with pseudopods on its surface.^{58,75}

E. histolytica is the pathogenic ameba that can cause invasive intestinal and extraintestinal disease. The most frequent manifestations of invasive amebiasis are colitis and liver abscesses. *E. histolytica* invades the colonic mucosa, and the patient suffers from bloody diarrhea. It is one of the most common parasitic infections worldwide, and the possibility of amebiasis must always be considered in a patient who complains of bloody diarrhea and has recently returned from a developing country. In industrialized countries where the *E. histolytica* endemicity is generally low, invasive disease may occur in men who have sex with men.⁷⁶ In tissues, the trophozoites—with a basophilic and elongated cytoplasm, single eccentric nucleus, and central spherical karyosome—are difficult to observe. In cutaneous and mucosal lesions, they are more easily seen in biopsies of the borders rather than the center of the ulcer.⁵⁸

E. histolytica is a pathogenic ameba with an increased risk for creating invasive amebiasis among persons with HIV.⁶⁰ The infestation by this species is a public health concern, because it has the potential to become endemic and to cause severe disease, with acute dysenteric symptoms and signs (malaise, fever, abdominal pain, and frequent loose stools containing blood and mucus); granulomatous masses in the bowel wall (ameboma); liver abscess; and pleura, lung, and pericardium involvement.⁷⁷

Vegetative forms of amebae should be sought in fresh stools or in scrapings from gastrointestinal ulcers at sigmoidoscopy. Ultrasound, computed tomography, and aspiration may be used in diagnosing a suspected liver abscess.

Patients can be rapidly cured in 7–20 days with metronidazole, 20–40 mg/kg/day, divided in three daily doses, for up to 8 days. Tinidazole, in a single daily dosage, 2 g for adults and 50–60 mg/kg for children, for 3–5 days, also shows rapid results. IV or intramuscular dehydroemetine hydrochloride, the drug of choice in the past, is cardiotoxic. Diiodohydroxyquinoline, paromomycin, and diloxanide furoate can also be used. Severe dysentery associated with mucosal or cutaneous involvement requires support measures.^{59,64,78} Auranofin, a gold-containing compound originally approved to treat rheumatoid arthritis, has activity against trophozoites of *E. histolytica* due to its monovalent gold molecule that readily inhibits *E. histolytica* thioredoxin reductase.⁷⁹

Mucocutaneous Leishmaniasis

Leishmaniasis is an anthroponosis of worldwide distribution, being considered a public health problem in 88 countries, distributed in four continents, in the Americas, Europe, Africa, and Asia. On the American continent, there are records of cases from the extreme southern part of the United States to north of Argentina, with the exception of Chile and Uruguay.^{24,64,75,77,80}

Leishmania belongs to the Trypanosomatidae family of protozoa. It is an obligatory intracellular parasite of the mononuclear phagocyte system, with two main forms: a flagellated or promastigote, observed in the digestive tube of the vector insect, and another aflagellated or amastigote, found in the tissues of vertebrate hosts. Currently in the Americas, there are 11 known dermatropic species of *Leishmania* causative of disease in humans and eight species described only in animals, all belonging to the subgenera *Viannia* and *Leishmania*. The three main species are *L.(V.) braziliensis*, *L.(V.) guyanensis*, and *L.(L.) amazonensis*.^{64,80}

The vectors are insects called Phlebotominae, belonging to the order Diptera, family *Psychodidae*, subfamily *Phlebotominae*, genus *Lutzomyia*, also known popularly as sandflies, and, depending on the geographical location in Brazil, as *mosquito palha*, *tatuquira*, and *birigui*, among others. The reservoirs can be forest animals (such as rodents and marsupials), synanthropic and domestic (canidae, felidae, and equidae, considered accidental hosts of the disease).⁶⁴

Transmission occurs through a sting without distinction regarding sex, race, or age, and without person-to-person transmission. The majority of cases occur in men between 20 and 40 years old. The incubation period in humans may vary from 2 weeks to 2 years, with an average of 2–3 months.^{57,65} Epidemiologic analyses have suggested changes in the transmission pattern of the disease passing from a sylvestral animal zoonosis to a disease of rural zones, in practically barren and periurban areas. There are three epidemiological profiles: sylvestral, in which the transmission occurs in areas of primary vegetation (zoonosis of sylvestral animals); occupational, associated with irregular forest exploration and forest slashing (anthroponosis); and rural or periurban, in areas around cities or colonized regions, where the vector undergoes an adaptation to the peridomicile (zoonosis of residual woods and/or anthroponosis).⁶⁴

The transmission cycles differ according to the geographic variations, involving several types of parasites, vectors,

reservoirs, and hosts. *L. (L.) amazonensis* is present in primary and secondary forests of the “Legal Amazonia” (Amazonas, Pará, Roraima, Tocantins, and Maranhão), and also in the states of the Northeast Region (Bahia), Southwest (Minas Gerais and São Paulo), Midwest (Goiás), and South (Paraná) of Brazil. It causes localized cutaneous ulcers and, occasionally, some individuals can develop a classic diffuse cutaneous leishmaniasis. *L. (V.) guyanensis* is found in onshore forests and is apparently restricted to the North Region of Brazil (Acre, Amapá, Roraima, Amazonas, and Pará) and Guyana, Suriname, and French Guiana. There may be single or multiple cutaneous ulcers, with the latter resulting from simultaneous stings of several infected phlebotoma or secondary lymphatic metastases. Mucous involvement is rare. In endemic areas, besides young men, a great number of children can be affected. *L. (V.) braziliensis* is a widespread species, occurring from Central America and all over Brazil to the North of Argentina. In the areas of modified environments, transmission occurs in the surroundings of the dwellings, affecting individuals of both genders and all age groups, with a tendency to concentrate the cases in a single focus. The lesions that are characterized by cutaneous ulcer (single or multiple) or the main complication, which is hematogenous metastasis to the mucous membranes of the nasopharynx, with tissue destruction, can occur in the eyelids or in areas usually covered by clothes, suggesting that the transmission with great frequency occurs inside human dwellings.^{64,80}

When introduced into the skin, promastigotes meet the immune system cells, as T and B lymphocytes, macrophages, Langerhans cells, and mastocytes. Through a not entirely clarified mechanism, the parasite adheres to the surface of the macrophages and Langerhans cells, passing into the intracellular media and changing into the amastigote form, characteristic of parasitism in mammals. The leishmania develop defense mechanisms capable of subverting the microbicidal capacity of the macrophages, surviving and multiplying until cell rupture occurs, when they are freed to infect other macrophages and propagate the infection. The location of the amastigote in the interior of macrophages makes the control of the infection become dependent on the immune response mediated by the cells. The main effecting cell is the macrophage itself, after its activation by T-helper lymphocyte cells. Even with the diversity of *Leishmania* species, the spectrum of clinical manifestations of the disease depends not only on the species involved, but also on the infected individual's immunologic state. With cutaneous leishmaniasis, the cutaneous test with leishmanin, the intradermal reaction of Montenegro (IDRM), and other in vitro tests are positive. Cutaneous leishmaniasis can be caused by all dermatropic species of *Leishmania*. There are clinical differences, however, such as those observed in lesions caused by *L. (L.) amazonensis* that present more infiltrated borders, with great amounts of parasites, whereas in those caused by the subgenus *Viannia*, few macrophages and parasites are present.^{64,75,80}

An infection is called unapparent when characterized by positive serologic and IDRM tests in apparently healthy individuals, living in areas of mucocutaneous leishmaniasis without previous clinical history. Lymph node leishmaniasis is characterized by localized lymphadenopathy without integumentary lesion. Cutaneous leishmaniasis presents as a rounded or oval painless ulcer, of few or several millimeters, located in exposed sites of the skin, with an erythematous and infiltrated base, with well-delimited and raised borders,



Figure 13.27 Leishmaniasis—ulcer on the side of the neck with a visible lymph-node enlargement.

reddish background, and coarse granulations (Figure 13.27). Vegetating lesions also occur, either papillomatous or verrucous, as well as lesions with associated bacterial infection (Figure 13.28). The lesions tend to cure spontaneously with



Figure 13.28 Leishmaniasis—vegetating lesion on the lip. (Reproduced with permission from Ramos-e-Silva M, De Moura Castro Jacques C. *Clin Dermatol* 2002;20:122–134.)

atrophic, depressed scars, with hypo- or hyperpigmentation and fibrosis in variable periods, but may remain active for several years and coexist with later emergence of mucous lesions. The disseminated mucocutaneous leishmaniasis form is relatively rare, being observed in up to 2% of the cases. The two species recognized as causes of this syndrome are *L. (V.) braziliensis* and *L. (L.) amazonensis*. There is emergence of multiple papular lesions with an acneiform aspect, on several segments of the body, mainly on the face and trunk, followed by hematogenous or lymphatic dissemination of the parasite, sometimes within 24 hours, causing distant lesions from the site of the sting. Concurrent mucous affection has been observed in up to 30% of the patients, and systemic manifestations can also appear, as fever, general indisposition, muscle pains, weight loss, and anorexia, among others.

Finding the parasite in the disseminated form is uncommon when compared to the diffuse form. The titers of serous anti-*Leishmania* antibodies are high, and the response to the IDRM is variable. In individuals coinfecting by HIV, ulcerated lesions prevail. The diffuse cutaneous form is severe, albeit rare, and occurs in patients with lack of energy and specific deficiency in the cellular immune response to *Leishmania* antigens. In Brazil, it is caused by *L. (L.) amazonensis*. The response to the therapeutics is poor or absent, and IDRM is usually negative. It is possible that 3%–5% of patients with cutaneous leishmaniasis may develop a painless mucous lesion, destructive of the upper respiratory tract due to hematic or lymphatic dissemination. Patients with multiple cutaneous, extensive lesions of more than 1 year's duration and located above the waist are the group with greater risk of developing metastases in the mucous membrane. The etiologic agent causative of mucosal lesions, in Brazil, is mainly *L. (V.) braziliensis*. IDRM is strongly positive; however, it has difficult parasitologic confirmation due to the scarceness of parasites, presents difficult therapeutic response, has a higher complication frequency, is mainly infectious, and may result in death in 1% of the cases.⁷⁵

The clinical-epidemiological diagnosis is complemented by positive IDRM. Direct demonstration of the parasite is the procedure of first choice because it is faster, less expensive, and easy to execute (Figure 13.29). The probability of finding

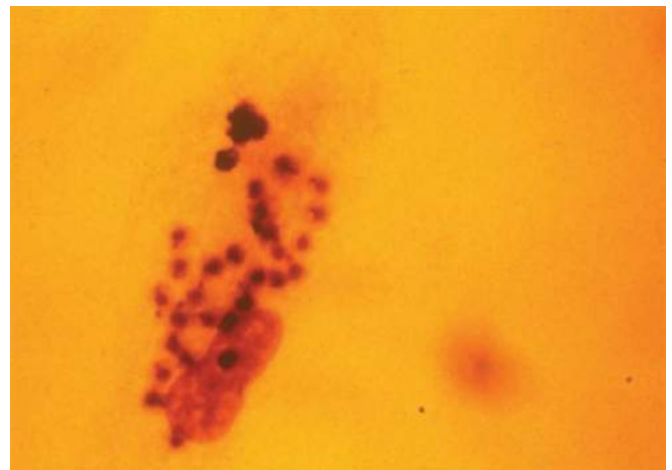


Figure 13.29 Leishmaniasis—amastigote inside a macrophage.

the parasite is inversely proportional to the time of evolution of the cutaneous lesion, being rare after a year. The isolation in cultivation *in vitro* is a method that allows the subsequent identification of the species of *Leishmania* involved. The intra-dermal test, IDRM, or leishmanin test is based on the response of retarded cellular hypersensitivity. Patients with mucous disease usually present an exacerbated IDRM, with several centimeters of hardening, vesiculation in the center of the reaction, possibly with ulceration and local necrosis. In diffuse cutaneous forms, IDRMs are usually negative. Other methods, such as detection of circulating antibodies and PCR, can also be used.^{77,80}

The drugs of first choice in the treatment of leishmaniasis are the pentavalent antimonials, considered as leishmanicidal drugs, because they interfere in the bioenergetic processes of the amastigote forms of *Leishmania*. Among antimonials side effects are cardiac conduction abnormalities and elevated serum transaminase and pancreatic enzyme levels being among the most serious. In the case of unsatisfactory response with pentavalent antimonials, the second choice of drugs is amphotericin B and pentamidines. Oral miltefosine, a phosphorylcholine ester of hexadecanol, originally used to treat cancer, has been shown as efficacious in treating both Old and New World cutaneous and visceral leishmaniasis. Another oral agent used is allopurinol, which inhibits purine anabolism in *Leishmania* and is less expensive and less toxic than the antimonials.⁸¹

The cure criterion is clinical, being recommended a regular follow-up for 12 months. Cure is defined by epithelization of the ulcerated lesions and total regression of the infiltration and erythema, up to 3 months after the end of treatment. Recurrence is defined as reappearance of the lesion in any part of the body in the period of up to 1 year after clinical cure, discarding the possibility of reinfection. Prophylactic measures include the use of insect repellents; fine-mesh mosquito nets, the screening of doors and windows; and environmental handling through cleaning of backyards and land areas.^{64,75,77}

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Life-threatening stings, bites, and marine envenomations

Dirk M. Elston

BITES AND STINGS

Major causes of death related to arthropod bites and stings include anaphylaxis, reactions to venom, and vector-borne disease.

ANAPHYLAXIS

Background

Anaphylaxis related to insect stings is estimated to occur in 3 of every one hundred adults.

Clinical and Laboratory

Skin tests can be used to verify a history of sting allergy. Radioallergosorbent (RAST) testing is less sensitive but does not carry a risk of anaphylaxis during the testing. It is important to note that neither the size of a skin test reaction nor the RAST level is a reliable predictor of the severity of subsequent sting reactions.¹ In vitro methods of testing also include Western blot and in vitro basophil activation tests that measure histamine and sulphidoleukotrien released (CAST—Cellular Antigen Stimulation Test) or activation markers on the cell surface detected by means of flow cytometric analysis (Flow CAST).^{2,3} Basophil activation tests using either CD63 or CD203c show promise in the in vitro diagnosis of patients with bee or wasp venom allergy.⁴

Patients with mastocytosis who develop severe hypotension after wasp or bee stings typically do not demonstrate specific IgE. Similar patients have been described with no skin lesions to suggest mastocytosis. In some, serum tryptase elevations suggest subclinical mastocytosis, and bone marrow biopsy may reveal systemic mastocytosis.⁵

Cardiac medications such as beta blockers and angiotensin-converting enzyme (ACE) inhibitors may increase the severity of anaphylactic reactions, placing the patient at greater risk for a bad outcome.⁶ In contrast, previous large local reactions to insect stings do not increase the risk of subsequent anaphylaxis.⁷ In a study of 115 patients with a history of an anaphylactic reaction to a wasp sting and specific IgE to *Vespula* and/or *Polistes*, the mean age was higher in patients with no cutaneous symptoms and cardiovascular involvement was more frequent in males, but the clinical pattern was not predicted by a history of atopy.⁸

Vespid remain the major cause of insect-related anaphylaxis. In a retrospective review of 98 adult patients with anaphylactic reactions to vespids, 18 patients (18%) suffered a reaction to wasp venom while at work. The rest of the reactions occurred during leisure time. Most (94%) of the patients with work-related anaphylaxis had a personal history of atopy, while only 22% of those with sting-induced anaphylaxis outside of the workplace had an atopic diathesis. Previous systemic

reactions had occurred in 17% of the patients. Gardening was the occupation most closely associated with a risk of vespid-induced anaphylaxis. *Vespula* IgE was detected in all patients, and *Polistes* IgE was detected in 78%.⁹

Among patients with bumblebee allergy, two groups have been identified, those with IgE highly cross-reactive with honeybee venom and those frequently stung only by bumblebees, who require immunotherapy with purified bumblebee venom.¹⁰

Children with insect-induced anaphylaxis have a higher incidence of honeybee allergy than adults, but severe systemic reactions are less common than in adults. Those with moderate to severe systemic reactions have a 30% chance of a similar reaction years later. Fortunately, the long-term immune tolerance induced by immunotherapy is greater in children than adults.¹¹

Membranous winged insects other than wasps and bees can also cause anaphylaxis, most notably the fire ants *Solenopsis invicta* and *Solenopsis richteri*. A diverse array of other ant species belonging to six different subfamilies (Formicinae, Myrmecinae, Ponerinae, Ectatomminae, Myrmicinae, and Pseudomyrmecinae) have also been associated with anaphylactic reactions.¹² Although hymenopterids remain the major cause of arthropod-induced anaphylaxis, other arthropods, such as the European pigeon tick (*Argas reflexus*) have also been implicated. This tick has demonstrated the potential for both IgE-mediated sensitizations and anaphylactic reactions.¹³

Therapy

Although intramuscular injections of epinephrine remain the standard type of epinephrine therapy for vespid-related anaphylaxis, rapidly disintegrating sublingual epinephrine tablets show promise for oral treatment of anaphylaxis.^{14,15} Delays in administration of epinephrine are associated with an increased risk of mortality.¹⁶ Biphasic reactions are common, and patients need extended observation after their initial response to therapy.¹⁷ Desensitization improves quality of life and is preferred by patients.¹⁸ All patients with sting-related anaphylaxis should be referred to an allergist to discuss the option of desensitization. Venom immunotherapy is thought to be 75%–98% effective in preventing future episodes of anaphylaxis. Rush regimens of hymenoptera venom immunotherapy have been shown to be safe and effective.^{19,20}

Course and Prognosis

Risk factors for fatal anaphylactic reactions include preexisting cardiovascular disease and a high mast-cell load as evidenced by clinical evidence of mastocytosis or an elevated baseline

serum tryptase level.²¹ Patients with vespid allergy who also have mastocytosis are at greater risk for life-threatening sting reactions, but most tolerate venom immunotherapy well with few systemic symptoms.²²

VENOM

Background

A wide variety of reaction to arthropods relates directly to the venom. Manifestations vary from disseminate intravascular coagulation to rhabdomyolysis.

Clinical and Laboratory

Rhabdomyolysis with acute renal failure has been described after fire ant bites. Life-threatening facial edema has been reported after exposure to pine caterpillars. Neurologic symptoms are common after centipede bites but are usually self-limited. Acute myocardial infarction in a previously healthy young man has been reported after a centipede bite.

Death from scorpion envenomation relates to the potency of the toxin, the age of the patient and preexisting conditions such as heart disease. In some studies, all fatalities involved children younger than 10 years of age. In Bangkok, a strip of Teflon tape is wrapped around each piling supporting a house. This prevents scorpions from climbing the pilings and entering the house. It has reduced infant mortality related to scorpionism.

Tityus zulianus is a major cause of scorpionism in Latin America. *Mesobuthus tamulus* (the Indian red scorpion) is often associated with fatal envenomation. The toxin produces an autonomic storm and has been associated with bilateral cerebellar infarction.²³ Prazosin reverses the autonomic storm characteristic of Indian red scorpion envenomation and is superior to antivenin.²⁴

Brown spiders of the genus *Loxosceles* include *Loxosceles reclusa*, the brown recluse spider (Figure 14.1). All spiders in this genus are capable of producing dermonecrotic reactions, and may also produce disseminated intravascular coagulation.²⁵ A generalized vasculitic exanthem has also been described following *Loxosceles reclusa* envenomation.²⁶



Figure 14.1 Brown recluse spider. (This and the following figures were produced while the author was a full-time federal employee; they are in the public domain.)

Brown recluse spiders have three sets of eyes (rather than the usual four) and a characteristic violin-shaped marking on the dorsum of the cephalothorax. Sphingomyelinase D is the primary dermonecrotic factor. The toxin depletes clotting factors VIII, IX, XI, and XII and prolongs the activated partial thromboplastin time in a dose-dependent manner.²⁷ The venom induces rapid coagulation and occlusion of small capillaries, causing subsequent tissue necrosis. Enzyme-linked immunosorbent assay (ELISA) methods can be used for the diagnosis of loxoscelism with noninvasive tissue sampling.²⁸ Both tissue swabbing and hair pluck techniques have been used.

Immunologic studies have demonstrated cross-reactivity between *L. boneti* and *L. reclusa* venoms, and between anti-*L. gaucho* and anti-*L. laeta* venoms. In contrast, the venom of South American *L. laeta* shows little cross-reactivity with North American *Loxosceles* antivenoms. This limits the worldwide distribution of spider antivenin.²⁹

Widow spiders are widely distributed throughout the world. Genetically, widow spiders can be divided into two large groups. The *geometricus* clade includes *Latrodectus rhodesiensis* from Africa, and the more widespread *L. geometricus*. The *mac-tans* clade contains all other *Latrodectus* species in Africa, the Middle East, the Iberian Peninsula, Australia, New Zealand, and North and South America.

Black widow spiders (Figure 14.2) are more toxic than brown widow spiders and are found throughout the continental United States and southern Canada. The venom contains latrotoxins that act by depolarizing neurons, resulting in increasing intracellular calcium and release of neurotransmitters. Female black widow spiders can be as much as 20 times larger than the males and have much more potent venom. The female can be identified by the red hourglass pattern on the ventral aspect of her large, shiny, roughly spherical abdomen. Alpha-latrotoxin induces release of acetylcholine, norepinephrine, dopamine, and enkephalin. The result is abdominal rigidity that may mimic an acute surgical abdomen and may cause priapism.³⁰

Widow spiders are named for their cannibalistic behavior. The female mates, then kills. Some do not even wait until mating is complete before taking the first bite from their mates. Some male *Latrodectus* spiders have developed strategies to prolong their survival long enough to maximize their chance of passing on their genes. Female redback spiders (*Latrodectus hasselti*) have paired sperm-storage organs that are inseminated



Figure 14.2 Black widow spider.



Figure 14.3 Male and female *Dermacentor andersoni*.

during two separate copulations. If a male can survive to copulate twice, he ensures the transmission of his genes. Males have developed a reflexive abdominal constriction during courtship that increases their chance of survival from cannibalistic injury inflicted during the first copulation.³¹ Hardly romantic, but effective nonetheless.

In a study of redback spider envenomation, the median duration of symptoms was 48 hours, with severe pain lasting more than 24 hours occurring in more than half of the patients. Systemic signs and symptoms occurred in more than one-third of the patients. Local diaphoresis and pain are characteristic features.

Australian funnel-web spiders (*Atrax* and *Hadronyche* spp.) pose a significant risk in Australia. They are not related to the funnel-web spiders (*Tegenaria agrestis*) of the Pacific Northwest. In a prospective Australian study of 750 spider bites with expert identification of the spider, clinically significant effects occurred in 44 bites (6%), including 37 of 56 redback spider bites. The major symptom was pain lasting >24 h. One severe neurotoxic envenomation by an Australian funnel-web spider required antivenin therapy.³² Brazilian *Phoneutria* “armed spiders” have a limited range but are an important cause of life-threatening bites in Brazil. Antivenins are available for both the neurotoxic Australian funnel-web spider and the Brazilian armed spider, but relatively little data exist regarding efficacy.

Lonomia caterpillars in South America cause a hemorrhagic diathesis. No antivenin exists. Tick paralysis in North America is typically associated with *Dermacentor* ticks. Tick paralysis typically occurs in children who present with rapidly progressive ascending paralysis. Symptoms resolve rapidly when the tick is removed, but *Dermacentor* ticks (Figure 14.3) tend to attach to the scalp where they are hidden by the hair. As a result, tick paralysis carries a death rate of approximately 10%. *Ixodes* tick paralysis is a common cause of death in Australian dogs, but is less likely to affect humans.

Therapy

Although in vitro data and rabbit studies suggest that dapsone and tetracyclines³³ could be of benefit in the treatment of brown recluse bites, a “real-life” delay in the onset of therapy negates any beneficial effect of dapsone therapy. In a rabbit model, the

only therapy that showed a trend toward less thrombosis in a rabbit model was intralesional triamcinolone.³⁴

The primary treatment for black widow spider envenomation is the administration of antivenin, although antispasmodics such as valium and calcium gluconate play some role. The antivenin is horse serum, and serum sickness can result from subsequent use. A new purified F(ab)₂ fragment, *Latrodectus mactans* antivenom, shows promise.³⁵

Redback spider antivenin is very effective at controlling local symptoms but did not demonstrate a conclusive effect against systemic toxicity.³⁶ It should be noted that redback antivenin is routinely given intramuscularly, which may not be as effective as the intravenous route.³⁷

VECTOR-BORNE DISEASE

Background

Arthropod-borne diseases remain a serious threat throughout most of the world. Malaria remains the single most important vector-borne disease and kills thousands every year. Other important vector-borne diseases worldwide include viral encephalitis, viral hemorrhagic fevers, African and New World types of trypanosomiasis, and leishmaniasis. In the United States, mosquitoes are more likely to carry West Nile fever, St. Louis encephalitis, equine encephalitis, or dengue. North American ticks are important vectors of Lyme disease (Figure 14.4), Rocky Mountain spotted fever, ehrlichiosis, Colorado tick fever, relapsing fever, tularemia, and babesiosis. Travel and climate change have affected the epidemiology of vector-borne diseases.^{38,39}

Clinical and Laboratory

Those in the developing world are at particular risk for transmission of arthropod-borne diseases. This is partly due to sophisticated vector-control programs in developed countries, and partly because of the indoor, air-conditioned lifestyle common to subtropical areas of the developed world. An outbreak of dengue along the U.S.-Mexican border demonstrated this effect. Disease transmission was greater on the Mexican side of the border, even though the vector was more abundant on the Texas side.⁴⁰

Whereas mosquito-borne illness predominates in much of the world, tick-borne illness is more common in



Figure 14.4 Erythema migrans of Lyme disease.

North America, Northern Europe, and even parts of Africa. *Amblyomma* ticks carry *Ehrlichia chaffeensis*, the agent of human monocytic ehrlichiosis, as well as Rocky Mountain spotted fever and southern tick-associated rash illness (southern Lyme disease), as well as African tick bite fever. *Dermacentor variabilis* is the major North American vector for Rocky Mountain spotted fever (RMSF). *Dermacentor andersoni* also carries RMSF and serves as a vector for Colorado tick fever, Q fever, and tularemia. Rocky Mountain spotted fever carries a high mortality rate if antibiotic therapy is delayed. In endemic areas, it is best to "treat now and ask questions later" for any patient with fever and a headache regardless of a history of tick bite. Spotless fever is particularly prone to misdiagnosis, and treatment should never be delayed due to the absence of rash.

Rhipicephalus ticks are common brown dog ticks in both North America and Europe. They are important vectors for RMSF as well as canine ehrlichiosis, Boutonneuse fever, babesiosis, and Congo-Crimean hemorrhagic fever virus. *Ixodes* ticks carry Lyme disease, babesiosis, anaplasmosis (human granulocytic ehrlichiosis), and viral encephalitis.

Trombiculid mites are important vectors of scrub typhus in East Asia and rickettsial pox is transmitted by *Liponyssoides sanguineus* (the house mouse mite). Body lice are important vectors for bartonella endocarditis among the homeless in urban areas.⁴¹ Fleas are important vectors of plague, bacillary angiomatosis, and endemic typhus.

Therapy

Most tick-borne diseases respond readily to tetracycline, with viral fevers and babesiosis being notable exceptions. Antibiotic prophylaxis after tick bites is controversial. Although it is not indicated after most tick attachments, an argument can be made for prophylaxis in highly endemic areas with ticks that are heavily engorged, evidence that they have been attached long enough to transmit disease.

Primary prevention of vector-borne disease requires a multifaceted approach including infrastructure measure for control of important vectors, use of screen and mosquito netting, and personal protection with repellents. Prompt tick removal also plays an important role in disease prevention. Secondary prevention of disease and morbidity can be accomplished with malaria chemoprophylaxis, prophylactic antibiotics after a tick bite, or early treatment of illness. Although malaria chemoprophylaxis may be reasonable for visitors to an area, it is not feasible for the entire indigenous population. Malaria-carrying anopheline mosquitoes feed mostly at night, emphasizing the importance of screen and mosquito netting. Screening can be impregnated with pyrethroids to improve their effectiveness. Because the mosquitoes that carry Dengue typically bite during the day, vector control, repellents, and protective clothing play important roles in disease prevention.^{42,43}

Infrastructure changes to control mosquito vectors include drainage of stagnant water, stocking of water with fish or turtles to eat larvae, spraying with insecticide, and gas- or electric-powered mosquito traps. Most mosquito traps generate carbon dioxide. Some use chemical attractants such as octenol and butanone in areas with *Aedes* mosquitoes, but it should be noted that some *Culex* mosquitoes are repelled by octenol.⁴⁴⁻⁴⁶

N,N-diethyl-3-methylbenzamide (DEET) remains the most commonly used repellent, although picaridin is gaining market share. Although DEET has a long safety record, rare cases of bullous dermatitis, anaphylaxis, and toxic encephalopathy

have been reported.⁴⁷⁻⁵⁰ For children, the American Academy of Pediatrics recommends slow release products that require less frequent application. They note that such products plateau in efficacy at concentrations of 30% and that there is no published evidence to support the use of higher concentrations in children. It should be noted that many extended duration products formulated for children have concentrations of 10% or less and that these appear to be perfectly adequate in most instances.

DEET products can generally be applied to both exposed skin and clothing, but permethrin products are to be applied to fabric. The combination of a DEET repellent and permethrin-treated clothing is effective against a wide range of biting arthropods.^{51,52}

Picaridin has been used in Europe and Australia and is now available in North America. In tests, it has shown good efficacy against a range of mosquitoes. A soybean oil-based product (marketed as Bite Blocker for Kids in the United States) shows reasonable efficacy against some mosquitoes and may be a good choice for those who wish to avoid chemical repellents. Neem oil products perform reasonably well against various mosquitoes, whereas citronella has limited efficacy.^{53,54}

Permethrin-treated clothing offers significant protection against ticks and chiggers, with good substantivity through a number of wash cycles.^{51,52,55} In southwest Asia and North Africa, some ticks are attracted by permethrin, but this has not been reported in other areas.⁵⁶

Deer fencing, border beds, insecticidal sprays, and even fire ants help keep residential and recreational areas free of ticks.^{57,58} Area sprays of insecticides are more effective once leaf debris is removed. Removal of leaf debris also reduces tick numbers by means of dehydration. Various other methods have been employed, including deer feeding stations outfitted to deliver topical acaricides to the deer. This approach is more cost-effective than adding a systemic acaricide to the deer corn.

MARINE ENVENOMATIONS Background

Marine animals contain some of the most potent toxins known.⁵⁹ Most minor envenomations result in severe pain. As the toxins tend to be heat-labile, emersion in hot, but not scalding, water is the preferred form of therapy. This section will focus on the more severe life-threatening envenomations.^{60,61}

Clinical Features

Chironex fleckeri, the Pacific box jellyfish or sea wasp, is responsible for many deaths as a result of shock and drowning. Confirmation of envenomation can be made by identification of the jelly or by means of tape stripping of nematocysts from skin.⁶² Other jellies cause painful eruptions but are much less likely to result in serious reactions. Important jellies around the world include *Physalia physalis*, the Portuguese man of war, endemic to the southern waters of the Atlantic, *Physalia utriculus*, the Pacific blue bottle jellyfish, as well as *Cyanea* and *Chrysaora* sea nettles. These may cause severe allergic reactions in some individuals, but generally lack the severe toxicity associated with *Chironex fleckeri*. All jellyfish produce serpiginous patterns of stings that follow the course of the tentacles attached to skin.

Sponge dermatitis is related to calcium and silica spicules that become embedded in the skin, and is rarely life-threatening. In contrast, sponge diver's disease is not caused

by the sponge at all, but rather by sea anemones attached to the base of the sponge. In addition to local symptoms similar to jellyfish stings, systemic symptoms may occur, such as nausea, vomiting, and headache. More severe reactions are possible in predisposed individuals.

Life-threatening envenomation by mollusks may occur with the blue-ringed octopus and with some cone shells. The blue-ringed octopus is a small cephalopod (about 10 cm long) found in waters off the coast of Australia. The distinctive blue rings may cause some foolish divers to get too close to the mollusk, but most envenomations occur completely by accident. Cone shells are marine gastropods with pretty shells, and a highly potent venom. The mortality rate may approach 20%. The shells are approximately 10 cm in length and tend to be found in shallow water, mostly in tropical and subtropical waters.

Death has been reported after penetrating chest injury from stingrays. The death may occur as a direct result of the inject or by means of venom-induced myocardial necrosis.⁶³ Envenomation by stonefish and lionfish is becoming more common as the fish move from tropical waters to a much more cosmopolitan distribution. Stings commonly result in pain, erythema, bulla formation, and tissue necrosis. Systemic symptoms may be life-threatening, but death is more likely a result of drowning related to disorientation following the sting. Catfish spine injuries may be associated with local pain, severe bleeding, and systemic symptoms, but they are rarely fatal.

Treatment

As with other bites and stings, knowledge and avoidance are the best means of preventing injury. Drowning is the most common cause of death from marine envenomation, and the swimmer should be removed from the water immediately. Irukandji syndrome is a poorly defined set of symptoms that occur after jellyfish envenomation and may include headaches, severe pain, nausea and vomiting, pulmonary edema, cardiac failure, and severe hypertension.⁶⁴ Supportive treatment for shock may be necessary in severe envenomations. Initial treatment for most marine envenomations includes soaking the site in hot, but not scalding, water to denature as much of the venom as possible. Sea wasp antivenin is available, but data on other systemic agents, such as calcium channel blockers are mixed. Physicians in coastal areas should consult current recommendations for treatment of local venomous species.

Course and Prognosis

The prognosis depends on the potency of the toxicity, comorbidities such as cardiac disease or hypertension, and prompt removal from the water to prevent drowning.

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Severe and acute adverse cutaneous drug reactions I: Stevens–Johnson syndrome and toxic epidermal necrolysis

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INTRODUCTION

Adverse cutaneous drug reactions (ADRs) are frequent, affecting 2%–3% of all hospitalized patients. Fortunately, only about 2% of ADRs are severe and very few are fatal.

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute, severe, life-threatening diseases with a mortality rate reaching 30%, and only prompt recognition and diagnosis, along with referral to an intensive care unit or burn care unit might improve the prognosis and save the patient's life.

Historical Background

In his classic 1866 treatise "On Disease of the Skin," Ferdinand von Hebra (1816–1880) precisely described and gave the name to erythema multiforme.¹ In 1922, two American physicians, Albert Mason Stevens (1884–1945) and Frank Chambliss Johnson (1894–1934), described two patients, boys aged 7 and 8 years, who had "an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa, and severe purulent conjunctivitis"² that was later given the name "Stevens–Johnson syndrome." In 1950, Bernard A. Thomas divided EM into two categories: erythema multiforme minor (von Hebra) and erythema multiforme major, also known as Stevens–Johnson syndrome (SJS).³ In 1956, Alan Lyell (1917–2007) wrote the most highly cited contribution ever to appear in *The British Journal of Dermatology*: he described four patients with a scalding disease, which was later given the name toxic epidermal necrolysis (TEN), or the Lyell syndrome or Lyell disease.^{4,5} These severe, acute, life-threatening ADR were not classified and defined according to their clinical appearance and linked to their etiology and prognosis until around 1993.⁶

Definition and Classification

EM was initially described as an acute self-limited skin disease, symmetrically distributed on the extremities with typical concentric "target" lesions and often recurrent.¹ The terminology "EM minor" was later proposed to separate the mild cutaneous syndrome from more severe forms with involvement of several mucous membranes, "EM major." SJS had for years been considered an extreme variant of EM, and TEN as being a different entity. In 1993,⁶ a group of contemporary experts proposed a new classification in which they separated SJS from the EM spectrum and added it to TEN, thereby creating a new spectrum of drug-related severe diseases, e.g., SJS/TEN. Two disease spectra were created: (1) EM consisting of EM minor and EM major and (2) SJS/TEN. The former are often recurrent, postinfectious disorders (especially herpes and mycoplasma) with low morbidity and almost no mortality. The latter are

usually severe drug-induced reactions with high morbidity and poor prognosis.

According to the new "consensus definition and classification,"⁶ categorization of these diseases is determined essentially by the percentage of skin detachment (Figures 15.1 and 15.2) and by the characteristic appearance of the typical individual "EM-like" or "target" lesions.

The clinical pattern of the individual skin lesion was classified into four different types:

1. *Typical targets*—individual lesions less than 3 cm in diameter with a regular round shape, well-defined border, and at least three different zones, i.e., two concentric rings around a central disk. One ring consists of palpable edema, paler than the center disk.
2. *Raised atypical targets*—round, edematous, palpable lesions, similar to EM but with only two zones and/or a poorly defined border.
3. *Flat atypical targets*—round lesions characteristic of EM but with only two zones and/or a poorly defined border and nonpalpable with the exception of a potential central blister.
4. *Macules with or without blisters*—nonpalpable, erythematous, or purpuric macules with an irregular shape and size and often confluent. Blisters often occur on all or part of the macule.

The involved body surface area (BSA) should measure the extent of detached and detachable epidermis (which is often much less than the area of erythema) at the worst stage of the disease.

These authors then proposed the following consensus classification into five categories:

1. *EM*—detachment <10% of BSA, localized typical targets or raised atypical targets
2. *SJS*—detachment <10% of BSA, widespread erythematous or purpuric macules or flat atypical targets
3. *Overlap SJS/TEN*—detachment between 10% and 30% of BSA, widespread purpuric macules or flat atypical targets
4. *TEN with spots*—detachment >30% of BSA, widespread purpuric macules or flat atypical targets
5. *TEN without spots*—detachment >10% of BSA, large epidermal sheets and no purpuric macules

They went on to suggest a practical algorithm in the definition and categorization of these diseases based on their classification. The first question the clinician needs to ask is: "What



Figure 15.1 A young woman with an eruption that would fit SJS.



Figure 15.2 Here she is 1 week later with a detachment area of nearly 90%. There were absolutely no drugs in her history. She had eaten shrimp the evening before.

is the percent of detachment?" The second question is: "What is the nature of the discrete lesions?" They also suggested that their purely descriptive clinical classification might indicate a causative agent, namely, that SJS, TEN, and overlap are drug induced, while the diseases in the EM group are due to infectious agents.

Because the involved area of detachment is defined as such at the worst stage of the disease, it cannot always be delineated when the clinician first sees the patient. Consequently, the most—and often the only—reliable means of classifying the cases is through observing the pattern of the individual lesions.

We⁷ recently proposed a small modification of the current classification to enable the clinician to pinpoint quickly and precisely the type of lesion to implement the appropriate treatment without delay.

Table 15.1 Original Classification

EM	SJS/Overlap/TEN
Typical targets	Flat atypical targets
Raised atypical targets	Macules with/without blisters

Table 15.2 Proposed New Classification

EM	SJS/Overlap/TEN
Raised typical targets	Flat typical targets
Raised atypical targets	Flat atypical targets
	Macules with/without blisters

We have noticed that patients of the SJS/TEN group occasionally also have typical targets that are flat and are missing the palpable ring around the center. We therefore suggested adding an additional type of lesion to the nomenclature, namely flat typical targets, and call the original typical targets as raised typical targets. The new classification will thus contain five types of lesions, instead of four (Tables 15.1 and 15.2).

As to the questions, why a new classification? Why an additional type of lesion that at first glance seems only to complicate the existing classification and make it more cumbersome? We contend that our proposed modification gives the classification better leeway incorporating all the variations characteristic of these lesions. We also believe that the new addition makes the classification more compact, easier to understand, and not less importantly, easier to remember. How can extending a classification make it more compact? In our proposed modified classification, all the lesions that are found in the EM group are raised, whereas all lesions that characterize the SJS/TEN group are flat. Accordingly, if a patient is found to have raised lesions (raised typical or raised atypical targets), we are directed toward a diagnosis of postinfectious EM. On the other hand, if a patient has flat lesions (flat typical targets, flat atypical targets, or macules with or without blisters), we should straight-away consider the diagnosis of drug-induced SJS/TEN.

Clinical Pattern

The initial symptoms of TEN, i.e., before the appearance of frank mucocutaneous sloughing, include fever (all cases) as well as conjunctivitis (32% of cases), pharyngitis (25% of cases), and pruritus (28% of cases). These signs usually last 2–3 days and can resemble an upper-respiratory infection. There is speculation that the fever is caused by drugs or release of pyrogens from epidermal necrosis, or both, but that it is not due to infection. Mucous membranes (in increasing order of frequency: oropharynx, eyes, genitalia, anus) are commonly affected 1–3 days before the skin lesions appear.⁸ The cutaneous lesions begin with a burning and painful eruption initially not typical. This eruption extends symmetrically from the face and upper part of the body to the entire body, predominantly on the trunk and proximal limbs. The initial lesions are poorly defined macules with darker centers. Maximal extension of lesions usually occurs in 2 or 3 days but can be manifest in a few hours. There is a sheetlike loss of epidermis and the appearance of flaccid blisters that spread with pressure. Nikolsky sign is positive over large areas involved by confluent erythema. Traumatized sites leave a dark red, oozing dermis. The entire skin surface may be involved, with up to 100% of epidermal sloughing. Widespread painful mucosal erosions result in impaired alimentation,

photophobia, and painful micturition. Keratitis and corneal erosions are less frequent, but they are known to occur. Asthenia, skin pain, and anxiety are extreme. Gastrointestinal or tracheobronchial epithelium can be involved via a process of necrosis resulting in profuse diarrhea or respiratory distress, respectively, and causing high morbidity.^{9,10} Prerenal azotemia is common. Fluid losses are massive and accompanied by electrolyte imbalance. During the first days, skin lesions are usually colonized by *Staphylococcus aureus*; they are later invaded by gram-negative rods. Thermoregulation is impaired, and energy expenditure is increased.^{11,12} Alteration of immunologic functions increases the risk of sepsis.

Reepidermization begins after a few days, and most of the skin surface is reepithelialized in 3 weeks. Pressure areas and mucosal lesions often remain eroded and crusted for two additional weeks. Scarring may occur in areas of pressure or infection. Disturbances in pigmentation are characteristically present and lead to a patchwork of pigmented and hypopigmented areas. Ocular sequelae are frequent and severe, affecting about 40% of the survivors.^{13,14} Abnormal nail regrowth, phimosis, and vaginal synechiae may be present as well.¹⁴

Differential Diagnosis

The above classification is intended to help physicians to differentiate EM from SJS/TEN; however, there are several other dermatoses that must be differentiated from these diseases.

Although the clinical presentation and patient history make the diagnosis of the classical form of SJS (with its target lesions and mucosal involvement) and of TEN obvious, other conditions should be considered in the differential diagnosis, particularly in the early stages of disease when the full-blown picture may not be fully apparent. These simulators include staphylococcal scalded skin syndrome (SSSS); linear IgA bullous dermatosis; paraneoplastic pemphigus, acute graft-versus-host disease (AGVHD); drug-induced pemphigus and pemphigoid, urticarial vasculitis, lupus erythematosus; Sweet syndrome, particularly the recently described variant of neutrophilic dermatosis of the dorsal hands. Linear IgA bullous dermatosis, SSSS, and drug-induced pemphigus usually do not show mucosal membrane involvement. All other diseases, except SSSS, Sweet syndrome, and AGVHD are not accompanied by fever.

In any event, two biopsy specimens are recommended, one for routine, formalin-fixed hematoxylin and eosin processing, and the other for immediate frozen sections. Epidermis must be present to make the diagnosis, as epidermal necrosis is the pathognomonic finding in this entity.

Laboratory Changes

Blood abnormalities are also almost always present. Anemia and lymphopenia are found in virtually all patients, neutropenia in 30% of patients (indicating a poor prognosis), and thrombocytopenia in 15% of patients.¹⁵ The peculiarity of the anemia lies in its aregenerative character, with concomitant medullary erythroblastopenia and blood reticulocytopenia. It does not appear to be secondary to the inflammatory process, because the regenerative capacity returns before the peak of the inflammatory phase. Lymphopenia is also commonly present (90% of patients) due to depletion of CD4+ helper T lymphocytes.^{16,17} Disseminated intravascular coagulation has been reported, and some authors advocate prophylactic treatment with heparin.¹⁸

About 30% of the patients have elevated transaminase enzymes¹⁹ and elevated levels of amylase and lipase without other evidence of pancreatic involvement.²⁰

Proteinuria is present in more than half of the patients, but usually at a level <1 g/24 hr. Renal tubular enzyme secretion and microalbuminuria are increased in all patients, but the glomerular filtration rate remains normal. This profile is suggestive of both proximal tubule involvement and secondary effects of glomerular structure.²¹

Causative Drugs

Drugs are clearly the leading causative factor and are associated with nearly 90% of TEN cases and over 50% of SJS cases.²²

The risk of drugs inducing SJS/TEN has been recently classified based on data from the RegiSCAR/EuroSCAR study, a prospective case-control study of risk factors.^{23,24} According to this classification, the high-risk drugs are allopurinol, carbamazepine, anti-infective sulfonamides, lamotrigine, phenobarbital, phenytoin, nevirapine, and selected nonsteroidal antiinflammatory drugs (NSAIDs—oxicam type). Moderate-risk drugs are cephalosporins, macrolides, quinolones, tetracyclines, and other NSAIDs (acetic acid type, diclofenac).

Pharmacogenomics of Adverse Drug Reactions

Notably, only a small number of patients exposed to the high-risk drugs develop the disease, and a genetic susceptibility has been suggested. Additionally, an association with human leukocyte antigen (HLA) had been reported more than 20 years ago.^{25,26}

A very strong association between the HLA allele HLA-B*15:02 and carbamazepine-induced SJS/TEN (CBZ-SJS/TEN) is now well known, especially among Han Chinese and Southeast Asians, of whom up to 15% are genetic carriers.^{27–29} Screening for HLA-B*15:02 in individuals of Chinese and Southeast Asian descent has been recommended by drug regulatory agencies, such as the U.S. Food and Drug Administration and the UK Medicines and Healthcare Products Regulatory Agency, a recommendation supported by international practice guidelines.³⁰ That association is missing in populations where HLA-B*15:02 is not prevalent. It is reasonable to postulate that other HLA alleles may also be involved in CBZ-SJS/TEN in different ethnicities. HLA-B*1511, which is a member of the HLA-B75 family, as is CBZ-SJS/TEN, is considered to be a risk factor for CBZ-SJS/TEN in Japanese and Korean populations.³¹

In 2005, HLA-B*5801 was found to be associated with allopurinol-induced SJS/TEN in Han Chinese individuals,³² and subsequently among people of Thai, Japanese, and Korean descent.³³ This has also been supported in a recent systematic review.³⁴

A European multicenter study found that HLA-B*5801 was present in 61% of patients with SJS/TEN, but only 55% of those of European ancestry.³⁵

Treatment

Both SJS and TEN are life-threatening diseases, and so the management of patients must be prompt. Early diagnosis with the early recognition and withdrawal of all potential causative drugs is essential to a favorable outcome. Morbidity and mortality decrease if the culprit drug is withdrawn no later than the day when blisters or erosions first occurred.³⁶

The patient must be transferred to an intensive care unit or a burn center. Prompt referral reduces risk of infection, mortality rate, and length of hospitalization.³⁶⁻³⁸ The conclusion of one literature review³⁹ was that "Most authors agree that because general principles of supportive management in TEN are similar to those in major burns, patients should be managed on a burns or intensive care unit." This generally accepted principle has been implemented during the last two decades. We⁴⁰ have challenged it and have suggested that SCAR patients would best be served by being cared for by a dermatologist, who should know more about cutaneous diseases than any other medical or surgical specialists. This is also the opinion of others⁴¹ who have recently come to the conclusion that "While burn centers are highly skilled in wound care, fluid management, and sepsis, they may not be as familiar with the management of the complex medical comorbidities in these groups of patients," and they have suggested that "dermatology hospitalists may become the optimal bridge to provide the differential diagnosis and wound care needed for these patients." They also supported our claim⁴⁰ that the "ideal model for the treatment of TEN patients is a special intensive care room within the department of dermatology staffed by dermatologists."

The main types of symptomatic treatment are the same as for burns, and the experience of burn units is helpful for the treatment of TEN: environmental temperature control, careful and aseptic handling, sterile field creation, avoidance of any adhesive material, and maintenance of venous peripheral access distant from affected areas.

Intravenous fluid replacement must be initiated immediately upon admission and using macromolecules or saline solutions. The rate and amount of fluid and electrolytes administration must be adjusted daily. The early fluid requirements of TEN patients are two-thirds to three-fourths of those of patients with burns covering the same area.⁴²

Like most other authors, we do not advocate the use of prophylactic antibiotics. Catheters should be changed and cultured regularly, and bacterial sampling of the skin lesions must be performed at least every 48 hours.

Early initiation of massive oral nutrition by nasogastric tube to minimize protein losses promotes healing and decreases the risk of stress ulcer.

The environmental temperature should be raised to 30°C, and heat shields, infrared lamps, and an air-fluidized bed should be provided.

Thromboembolism and disseminated intravascular coagulation are important causes of morbidity and death: effective anticoagulation with heparin is recommended for the duration of hospitalization.

Like patients with major burns, TEN patients suffer severe pain as well as emotional instability and extreme anxiety that should be treated appropriately.⁴²

Pulmonary care includes aerosols, bronchial aspiration, and physical therapy. Intubation and mechanical ventilation are nearly always necessary if the trachea and bronchi are involved.

The SJS/TEN disease spectrum remains an important cause of severe visual loss in a significant number of patients. Therefore, daily examination by an ophthalmologist and vigorous treatment are mandatory. Antiseptic or antibiotic eye drops and eye ointments, with or without corticosteroids, should be instilled every 2 hours. Lid-globe adhesions should be cautiously removed with a glass rod twice daily to avoid

occlusion of the fornices, taking care not to strip pseudomembranes, which may lead to bleeding and increased conjunctival scarring.⁴³

There is no consensus about topical care. Topical antiseptics (0.5% silver nitrate or 0.05% chlorhexidine) are usually used to paint, bathe, or dress the patients. Silver sulfadiazine, which is very popular in burn units, should be avoided, because sulfonamides are frequently implicated in the etiology of TEN and can cause hemolysis in G6PD-deficient patients. Although most surgeons of the burn units advocate large operative debridement of nonviable epidermis followed by immediate wound cover with biologic dressings such as Biobrane or xenograft,⁴⁴ dermatologists are more conservative, leaving in place the epidermis that has not yet peeled off. Nanocrystalline silver (NCS) has recently been suggested,⁴⁵ because it has good antimicrobial efficacy and is effective in modulating matrix metalloproteinases (MMPs), which have a destructive effect on the extracellular matrix and play a part in the epidermal/dermal cleavage seen with this disease. This dressing, however, needs operating room debridement and is therefore used only by plastic surgeons in burn centers. Dressings may be gauzes with petrolatum, silver nitrate, polyvidone iodine, hydrogels, Hydrone, Vigilon (semipermeable dressings) Soft-Sorb, and others that can also be impregnated with silver nitrate.

Corticosteroids and Other "Disease-Modifying" Drugs

Corticosteroids have for years been the mainstay therapy for TEN and SJS in most⁴⁶⁻⁵⁴ (although not all^{55,56}) dermatological centers, including ours, in the belief that they suppress the intensity of reaction, control the extension of the necrolytic process, decrease the involved area, reduce fever and discomfort, and prevent damage to internal organs when given at an early stage and in a sufficiently high dosage. There are no randomized clinical trials on the use of corticosteroids in the treatment of these life-threatening diseases.

The early approach to treatment was followed by a complete turnabout at the beginning of the 1980s when the management of SJS/TEN shifted to specialized burn centers and was taken over by nondermatologists, mostly surgeons, who rejected the use of steroids almost out of hand. They regarded them as being hazardous and a potential iatrogenic source of decreased host resistance, increased morbidity and complications (e.g., sepsis, leukopenia, thromboembolism, gastrointestinal ulcerations, etc.), prolonged recovery, worse and deteriorated prognosis, reduced survival, and for all intents and purposes, a contraindicated mode of therapy.⁵⁷⁻⁶²

In the absence of well-controlled trials, many dermatological departments adopted the concept of large burn units to avoid the use of steroids, in our opinion more as a matter of practicing "defensive medicine" and being on the safe (rather than on the effective) side.

Recently, it had been our impression that there has been a waning in the negative attitude toward steroids and the damaging and harmful effects attributed to them. Several authors have concluded that the general negative opinion of corticosteroids is probably because they had been given too late, in too low a dose, and for too long a period during the process. Corticosteroids may indeed impair wound healing and promote sepsis. As a result, we are now witnessing a new trend of treating TEN/SJS patients with high-dose pulse therapy with

dexamethasone (1.5 mg/kg daily) or prednisone (250–500 mg) over short periods (3 consecutive days), or an infusion of methylprednisolone at 1000 mg/d for 3 consecutive days and a second pulse of 500 mg/d for 2 consecutive days if symptoms persist, a protocol that has shown favorable results.^{63–67} Support for the use of corticosteroids has recently come from the publication of a large retrospective study⁶⁸ by some of the leaders in these diseases. They evaluated the effect on mortality from treatment administered after hospital admission in a cohort of 281 patients with SJS or TEN from France and Germany enrolled in the EuroSCAR study. Their findings confirmed what we already knew: specifically, that corticosteroids were more commonly used in Germany (87% of patients) than in France (45%). National differences in dosage were also observed, with a maximum dose of 250 mg (range, 120–500 mg) in Germany versus a maximum of 60 mg (range, 40–150 mg) in France. When the authors analyzed only patients with single-drug treatment, they observed a significant odds ratio for corticosteroids versus supportive care in Germany, but this was not validated by the outcomes in France. They suggested that their results were partly explained by the considerably higher dosage of corticosteroids in Germany.

Those authors, some of whom are known opponents of the use of steroids for these conditions, concluded that the results “do not support the prior opinion of many experts that corticosteroids were detrimental in the treatment of patients with SJS or TEN.” They continued by stating, “Only for corticosteroids is there a trend for a possible benefit, which is of further clinical interest; however, a prospective randomized trial is needed before any conclusion can be drawn.”⁶⁸

Whatever the differences of expert opinions in this issue, we still lack convincing evidence-based proof for the beneficial effects of corticosteroids in the treatment of TEN/SJS patients, and prospective randomized controlled studies are urgently needed. This is also the conclusion of a recently published review⁶⁹ of the current evidence for the use of steroids in adults presenting with TEN/SJS. It included only cohort studies with no case-control or cross-sectional studies, and found six studies that met their criteria. The conclusion was that “the impact that steroids have on mortality among patients presenting with SJS, TEN/SJS, and TEN is inconclusive.”

The main question that should be asked, however, is if we should wait until all the dust has settled around this issue and we have adequate substantiating evidence, or if we should go ahead and use steroids based on years of experience. The authors advocate using steroids.

Intravenous Immunoglobulin (IVIg)

In 1998, it was found that interaction between the death receptor Fas (CD95) and its ligand that is present on epidermal cells might be important in the apoptosis that characterizes TEN.⁷⁰ It was also demonstrated that high concentrations of normal Ig inhibit Fas-mediated apoptosis in sensitive cell lines.⁷⁰ The next step was a preliminary study on the treatment of TEN patients with high-dose IVIg. Ten patients with TEN were treated with IVIg at daily doses of 0.2–0.75 g/kg for 4 days. The survival rate was 100%, and there were no adverse effects.⁷⁰ Several other studies using IVIg to treat TEN have since been published, but with contradictory results.

A comprehensive search of the literature based on cohort studies and case series (excluding individual case reports)

yielded 17 relevant articles, 14 on TEN and three on SJS.⁷¹ Three of the TEN studies and one of the SJS studies were prospective, whereas the remaining 10 were retrospective in design. Eleven of the 14 TEN studies reported positive results; the other three failed to find a significant improvement with IVIg administration. Two of the three SJS studies reported positive results, but the third observed no significant differences in death, progression of detachment, or speed of reepidermalization. The authors of that review concluded that “IVIg appears to have a positive impact on the course of illness in individuals with TEN and SJS.”⁷¹

In a more recent metaanalysis⁷² the authors reached a similar conclusion, namely that “Intravenous IG at dosages of ≥ 2 g/kg appears to significantly decrease mortality in patients with SJS or TEN.”

The authors of the previously mentioned prospective study⁶⁸ on the effect of treatment administered after hospital admission on mortality rates in a cohort of 281 patients with SJS or TEN from France and Germany enrolled in the EuroSCAR study came to the opposite conclusion, namely, “To date, there is not sufficient evidence that any specific treatment is useful for patients with SJS or TEN. Especially for IVIg, this study demonstrates that the potential benefit of IVIg cannot be established.”

It is our hope that with the meteoric advances being made in biologic therapy and the continuing development of target monoclonal antibodies against cytokines and receptors, new therapies will emerge that will more selectively and specifically target the underlying processes, thus avoiding treatment-related side effects.

Prognosis

In the year 2000, a mathematical tool called SCORTEN was developed to assess severity of illness and predict mortality.⁷³ SCORTEN should be computed within the first 24 hours after admission and again on day 3.⁷⁴ The score is the sum of seven easily measured clinical variables: (1) age over 40; (2) tachycardia, $>120/\text{min}$; (3) the presence of malignancy; (4) initial surface of epidermal detachment $>10\%$; (5) serum urea $>10 \text{ mmol/L}$; (6) serum glucose $>14 \text{ mmol/L}$ ($>252 \text{ mg/dL}$); and (7) bicarbonate $<20 \text{ mmol/L}$ (mEq/L). One point is given for each variable if positive and zero if negative. Computing the sum of the scores for each parameter results in a “SCORTEN” ranging from 0 to 7, with the mortality increasing sharply with each additional point (Table 15.3).

The scoring system that was developed with a French-based patient cohort has been validated in a U.S.-based patient cohort⁷⁵ and is proving to be a valuable tool for predicting patient outcome.

A more recent study⁷⁶ investigated the risk factors for mortality up to 1 year after reaction, unlike other studies that assessed risk factors for death during hospitalization only.

Table 15.3 SCORTEN Predicted Mortality

SCORTEN	Mortality (%)
0–1	3.2
2	12.1
3	35.3
4	58.3
≥ 5	90.0

The former was based on the findings of 460 patients from the RegiSCAR (International Registry of Severe Cutaneous Adverse Reactions to drugs) study. Severity of reaction was a risk factor for mortality only in the first 90 days after onset, whereas serious comorbidities and age influenced mortality beyond 90 days and up to 1 year after the onset of reaction.

CONCLUSIONS

"Any substance that is capable of producing a therapeutic effect can also produce unwanted or adverse effects."⁷⁷ ADR had been reported since the beginning of ancient medicine. To our great fortune, the most severe ADR described herein SJS/TEN are very rare; however, despite their low incidence they are still frequent enough that primary care physicians and dermatologists will probably be involved with the management of at least one affected individual during their practice, but they are too infrequent for acquiring any real degree of familiarity with them.

There is no specific and definitely effective treatment for SJS/TEN, prompt recognition and diagnosis and early identification and withdrawal of all potential causative drugs, and prompt referral to a burn unit are generally agreed upon steps and, for the time being, the best we can do for our patients to most significantly influence outcome and prognosis. Beyond that, however, considerable controversy exists. Evidence both pro and con exists for the use of IVIG, systemic corticosteroid, and other measures.

In this chapter, we present practical and comprehensive information on two of the most severe acute cutaneous drug eruptions—SJS and TEN—concentrating on their definitions, classifications, clinical appearance, managements, and prognosis. It is intentionally very clinically oriented and covers what is most relevant to the clinicians in their practice, omitting the theoretical aspects of the pathogenesis of the diseases, unless they are relevant to diagnosis or treatment.

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Severe and acute adverse cutaneous drug reactions II: DRESS syndrome and serum sickness-like reaction

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DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

Background

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, formerly termed “drug hypersensitivity syndrome” (HSS), is a severe potentially fatal adverse drug reaction characterized by skin rash, fever, lymph node enlargement, and single or multiple organ involvement, characteristically occurring in a delayed fashion between 3 and 8 weeks after starting treatment with the culpable drug for the first time.

Phenytoin HSS was first described in 1939,¹ 1 year after phenytoin had been introduced in the treatment of convulsive disorders. Similar reactions were reported during the following years, initially to various anticonvulsant drugs^{2,3} and later to many other drugs.^{4–6} Consequently, the name of this reaction was changed to the more widely inclusive HSS, instead of anticonvulsant-, or sulfone-, or dapsone-hypersensitivity syndrome. The word “hypersensitivity” itself, however, is ambiguous and uninformative insofar as it may apply to any idiosyncratic reaction that fits one phase of the classic Gell and Coombs classification; therefore, a more informative, precise, and clinically relevant term was proposed, “drug rash with eosinophilia and systemic symptoms” or DRESS.⁷ The suitability of the term DRESS has been questioned, because eosinophilia need not necessarily be present in this syndrome, and a return to drug-induced HSS has been suggested.⁸

DRESS is characteristically defined by a triad of symptoms consisting of fever, skin eruption, and internal organ involvement. In this context, it should be mentioned that serum sickness (SS) or serum sickness-like reaction (SSLR), which have many common features with DRESS syndrome, are distinct diseases that have another pathogenesis and, as such, should be distinguished from DRESS syndrome (Table 16.1).

Epidemiology and Causative Drugs

The true incidence of DRESS syndrome is unknown, because its variable presentation confounds uniform diagnosis. It is estimated to occur in between one in 1000 and one in 10,000 exposures with drugs, such as anticonvulsants and sulfonamides.⁹ In a record linkage study, the risk for developing DRESS syndrome within 60 days of the first or second prescription in new adult users of phenytoin or carbamazepine was estimated to be 2.3–4.5 per 10,000 exposures, respectively.¹⁰

The aromatic anticonvulsants (phenylhydantoin, phenobarbital, carbamazepine)^{2,9,11–13} and sulfonamides¹⁴ are the most common causes of DRESS syndrome, but a large variety of other drugs have been associated with it, notably among them lamotrigine,^{11,12} allopurinol,^{15,16} nonsteroidal antiinflammatory

drugs, captopril, antibiotics tuberculostatic drugs, calcium channel blockers, mood stabilizers, neuroleptics, dapsone, terbinafine, methyldopa, minocycline, and antiretroviral drugs.^{17,18} Telaprevir, a protease inhibitor of chronic hepatitis, has been added to the drugs capable of DRESS induction.¹⁹

In a prospective study involving eight countries registered with RegiSCAR (a European commission funded registry for SCAR) 117 cases of DRESS were enrolled and analyzed, between 2003 and 2009.²⁰ Within this cohort drug causality was plausible in 88% of cases. Antiepileptic drugs were involved in 35%, allopurinol in 18%, antimicrobial sulfonamides and dapsone in 12%, and other antibiotics in 11%. The median time interval after drug intake was 22 days (interquartile range 17–31) for all drugs with (very) probable causality, with differences between drugs.

Pharmacogenomics of Adverse Drug Reactions

The role of genetic susceptibility as a risk factor for developing adverse drug reactions, and an association with human leukocyte antigen have been suggested decades ago.^{21,22}

HLA-A* 31:01 was reported to be associated with carbamazepine (CBZ)-induced SCAR, including SJS/TEN and DRESS. An international study²³ has shown a significant association of HLA-A* 31:01 with CBZ-DRESS in Europeans, and in Chinese. A metaanalysis of this study and other published studies presented in the same paper confirmed that in all populations, HLA-A* 31:01 had an extremely strong association with CBZ-DRESS.

A genetic predisposition and an association between HLA and allopurinol-associated severe hypersensitivity reactions have been suggested in southern Chinese patients more than two decades ago.²⁴ In a study from Taiwan, in 2005, HLA-B*5801 allele was present in all (100%) 51 patients with allopurinol-SCAR, 30 of them with DRESS, but only in 20 (15%) of 135 tolerant patients, thus confirming previous report.²⁵

Additional studies have confirmed this strong association between HLA-B*5801 and allopurinol-induced DRESS (and SCAR) in patients from China, Thailand, Hong Kong, and Korea (reviewed in Goncalo et al.²⁶). A slightly weaker association was observed in a European study with 63.2% of patients with allopurinol-induced DRESS carriers for HLA-B*5801.²⁶

Abacavir is a guanosine analogue associated with abacavir hypersensitivity syndrome in the premarketing phase of its development, characterized predominantly by fever, malaise, and gastrointestinal symptoms in up to 8% of those starting treatment; mild-moderate rash was a late feature. Unlike DRESS eosinophilia and hepatitis are uncommon (reviewed in

Table 16.1 Comparison between DRESS Syndrome and SS/SSLR

Symptom	DRESS syndrome	SS/SSLR
Rash	Exanthematous (mostly)	Urticarial (mostly)
Onset of symptoms	1–8 weeks	> 2 weeks
Fever	Present	Present
Internal organ involvement	Present	Absent
Arthralgia	Absent	Present
Lymphadenopathy	Present	Present

Pavlos et al.²⁷ and Mallal et al.²⁸). A strong association between HLA class I allele, HLA-B*5701, and abacavir hypersensitivity reaction was first reported in 2002. Later work improved the clinical diagnosis of true immunologically mediated abacavir hypersensitivity reaction through the use of patch testing. After this, a case-control study of black patients and of white patients in the United States demonstrated that 100% of both white patients and black patients with a positive patch test and with clinical history consistent with abacavir hypersensitivity reaction carried HLA-B*5701 (reviewed in Pavlos et al.²⁷ and Mallal et al.²⁸).

Clinical and Laboratory Aids Required for Diagnosis

DRESS syndrome occurs most frequently upon first exposure to the drug, with initial symptoms starting between 1 and 8 weeks afterward.² The syndrome may occur within 1 day upon rechallenge in previously sensitized individuals.

The syndrome commonly begins with a fever shortly followed by a maculopapular rash and varying degrees of lymphadenopathy. Body temperature ranges from 38°C to 40°C, with spikes that usually generate the concern of an underlying infection. The spiking fever often persists for as long as weeks despite discontinuation of the offending drug.²⁹

An eruption occurs in approximately 70%–100% of patients.⁸ In most cases, the cutaneous eruption starts as a macular erythema that often evolves into a red, symmetrical, pruritic, confluent, and papular rash. Pustules, either follicular or nonfollicular, may also be present. The upper portion of the trunk and the face are initially affected with later involvement of the lower extremities. Facial and periorbital edema is a frequent occurrence (Figure 16.1) and can lead to such gross distortion of the patients' features that they can become unrecognizable. Notably, there is usually no mucosal involvement, a feature that helps distinguish DRESS from other forms of severe drug eruptions, such as Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

As for internal organ involvement, again there is a large degree of variability among patients with regard to both the target organs involved and the severity of the involvement. It is important to emphasize, however, that the severity of cutaneous changes does not necessarily reflect the severity of internal organ involvement. Therefore, meticulous assessment is necessary for patients suspected of DRESS syndrome and internal organ involvement. It is also important to bear in mind that internal organ involvement may not develop for 1 to 2 weeks into the reaction, and even not until 1 month later.

The liver is the most frequently involved internal organ, with tender hepatomegaly and sometimes with splenomegaly. Liver involvement can range from mild elevations in serum transaminase levels³⁰ to granulomatous hepatitis or fulminant hepatic necrosis.^{31–34} The degree of hepatitis is related to the interval between the onset of the syndrome and the discontinuation of the drug.³⁵ Prompt recognition of the syndrome and withdrawal of the drug are, therefore, of utmost importance to the prognosis.

The kidney is another organ frequently involved, and the nephrotic condition can range from mild hematuria, to nephritis, to acute renal failure, usually following acute granulomatous interstitial nephritis, even despite discontinuation of the offending drug.^{36,37}

Rarer manifestations of DRESS syndrome are colitis, pneumonitis, pancreatitis, myocarditis, encephalitis, arthritis, and myositis.^{8,38} Thyroiditis with autoantibodies has also been reported. Its acute hyperthyroid phase may be missed by the clinician due to fever, tachycardia, and malaise, which are part of DRESS syndrome, and may thus be identified only several months later, when hypothyroidism develops.³⁹

An analysis of the spectrum of signs and symptoms of DRESS in a large multinational registry of SCAR, prospectively enrolled 201 potential cases from 2003 to mid-2009.²⁰ Next to the ubiquitous exanthema, hematologic abnormalities were present in 100% of the patients, eosinophilia in 95% of patients, visceral involvement in 91%, one organ involved in 36% of patients, two organs involved in 35%, more than two organs involved in 21%, liver involved in 75%, kidney in 37%, lung in 32%, muscle/heart in 13%, spleen in 15%, and pancreas in 4%.

In another retrospective cohort study in Taiwan using a DRESS database compiled from 2000 to 2013, 72 cases were evaluated.⁴⁰ Sixty-two patients' (86.1%) cases involved liver injury, in six of which (9.7%) were liver injury before skin presentation. The distribution of liver injury patterns at initial presentation



Figure 16.1 A 39-year-old man with carbamazepine-induced drug rash with eosinophilia and systemic symptoms (DRESS). Note the typical periorbital and forehead edema.

was 23 cholestatic type (37.1%), 17 mixed type (27.4%), and 12 hepatocellular type (19.4%). Patients with hepatocellular type were younger, with a median age of 31.5.

Lymphadenopathy is perhaps the most frequent finding associated with DRESS syndrome. In the early stages of the disease, lymph node histology shows benign hyperplasia, but histologic changes may progress to reveal atypical lymphoid cells and, in rare cases, pseudolymphoma or lymphoma may develop, if the drug is not discontinued.³⁵

Notably, no single symptom, including fever or peripheral eosinophilia, is necessarily present in all cases of DRESS, and cutaneous lesions apparently are, in fact, the most often reported signs. The clinical pattern of skin changes is, however, quite variable, ranging, according to the present definition, from a faint generalized exanthematous eruption to SJS or TEN. The same is true for the other associated symptoms, organ dysfunction, and laboratory abnormalities.^{8,38,41}

In 2006, a Japanese consensus group proposed a set of criteria for diagnosis of DRESS (or, as suggested by them, drug-induced hypersensitivity syndrome, DIHS).¹⁸ That group established six diagnostic criteria for DIHS/DRESS to which they subsequently added a seventh⁴²: (1) maculopapular rash developing 3 weeks or more after starting therapy; (2) prolonged clinical symptoms 2 weeks after discontinuation of the causative drug; (3) fever $>38^{\circ}\text{C}$; (4) at least one leukocyte abnormality, i.e., leukocytosis ($>11 \times 10^8/\text{L}$), atypical lymphocytosis ($>5\%$), or eosinophilia ($>1.5 \times 10^8/\text{L}$); (5) liver abnormalities (alanine aminotransferase [ALT] $>100 \text{ U/L}$), which can be replaced by other organ involvement, such as the kidney; (6) lymphadenopathy; and (7) human herpes virus 6 (HHV-6) reactivation. The diagnosis is confirmed by the presence of all seven of these criteria (*typical* DIHS) or of the first five (*atypical* DIHS). The most novel and innovative of the proposed criteria is undoubtedly HHV-6 reactivation. The authors state that their series of >60 patients, diagnosed by clinical findings, had consistently shown that HHV-6 reactivation can be detected in the vast majority of patients who satisfy the other six criteria and show clinical manifestations consistent with the classical triad, but not in patients with other types of drug eruption, such as papulomacular rash, SJS, and TEN. HHV-6 was rarely detected in patients with a tendency toward milder disease. Without entering into any debate about the appropriateness of this criterion, the fact that it usually appears 2–3 weeks after the onset of rash means that it can be used for studies and late analyses, but not when we first see our patient and have to make urgent decisions. The same holds true, of course, for their second criterion.

We especially espouse two features of this newly suggested classification: (1) it narrows the wide definition of cutaneous rash, in particular by excluding cases with cutaneous manifestations of SJS and TEN, a characteristic that we had emphasized long ago,^{17,41} and (2) it provides cutoff points for delineating hematological and other laboratory abnormalities.

Although most authors agree that the existence of DRESS as a clinically distinctive and unique entity is unarguable,^{8,43} its diagnosis is complicated because, in addition to its highly variable presentation, it is a diagnosis by exclusion. Its main features, such as rash, fever, and organ involvement, can also be attributed to a wide range of other causes, most notably infections (with which it is also often associated), and sepsis.^{44,45} This is of particular importance considering our efforts to avoid prescribing additional drugs for patients with DRESS, because they can cross-react with other drugs, or initiate drug

neosensitization⁴⁶ during DRESS, whereas we usually use drugs such as analgetics/antipyretics and antibiotics in the case of infections.

Treatment

DRESS is potentially life threatening. The mortality rate is estimated at nearly 10%, although complete recovery can be achieved.⁴⁷ DRESS syndrome must be promptly recognized and all potential culprit drugs withdrawn.

Skin care may include the use of topical steroids to alleviate clinical manifestations. The main principles of therapy for extensive rash or erythroderma are the same as for major burns: warming of the environment, correction of electrolyte disturbances, high caloric intake, and prevention of sepsis.

As for the controversy on the use of systemic corticosteroids, unlike their position on the administration of these medications to patients with SJS/TEN, most authors do not regard them as either hazardous or contraindicated and suggest their use “when internal organ involvement exists.”⁴⁸ Because internal organ involvement is a prerequisite for this syndrome (remember, the requisite triad of fever, rash, and internal organ involvement), systemic steroids should be considered in most cases of DRESS syndrome, particularly in those with severe organ damage.

In a retrospective study⁴⁹ of 38 cases of DRESS from a single center, the authors concluded that “Systemic steroids may not be required for the management of mild forms of DRESS, and may thus be reserved for more severe cases.”

Corticosteroids are known for their beneficial effects in diseases with blood eosinophilia (e.g., hypereosinophilic syndrome), where eosinophils are responsible for organ damage and thus might be expected to be of benefit in DRESS, insofar as eosinophil accumulation is also thought to account for the internal organ involvement in this disease.

SERUM-SICKNESS AND SSLR

Background

Serum sickness, first described in humans by Clemens von Pirquet (1874–1929) and Béla Schick (1877–1967) in 1905, is a type III hypersensitivity reaction (of the classic Gell and Coombs classification) resulting from the administration of foreign protein or of heterologous serum, usually equine, serving as an antitoxin.⁵⁰

The syndrome includes fever, cutaneous eruptions (mostly urticaria), edema, arthralgias, and lymphadenopathy. Although fatalities from this reaction are rare, it has been traditionally included in the group of severe adverse cutaneous reactions to drugs,⁵¹ because it requires hospitalization and often intensive care and might cause extensive organ damage.

During the first four decades of the nineteenth century, it was not uncommon for up to 50% of patients to develop this reaction after treatment with horse serum as an antiserum to diphtheria, tetanus, rabies, or other organisms. It has almost disappeared in these settings with the advent of effective immunization procedures, antimicrobial therapy, and the development of specific human immune serum globulins. More recently, serum sickness has made a comeback with the introduction of targeted immune modulators (TIMs)—commonly referred to as biological response modifiers or simply *biologics*. It is also commonly seen with the use of antivenom

therapy used to treat envenomations of snakes, spiders, scorpions, etc. The SSLR that is similar to classic serum sickness may result from the administration of a number of nonprotein drugs, such as antibiotics (particularly cefaclor and minocycline), psychiatric drugs, analgetic/antiinflammatory drugs, antineoplastic drugs, and many others.

Clinical and Laboratory Aids Required for Diagnosis

Early recognition and accurate diagnosis are the key to the management of serum sickness, because treatment is highly effective in reversing all symptoms. Recognition and diagnosis, however, are made more difficult by a lack of diagnostic and laboratory criteria and by the protean manifestations of this reaction.

An attempt has been made to gather signs and symptoms and produce diagnostic criteria for serum sickness.⁵² Four major criteria were established: (1) >7 days since initial drug (thymoglobulin) administration, (2) persistent high fevers (>101°F), (3) persistent arthritis/arthralgias, and (4) positive heterologous antibodies on ELISA. Rash was considered a minor criterion. These criteria are, however, in disagreement with earlier studies, in which the cutaneous rash appeared in more than 90% of patients.^{53–56} The clinical manifestations of serum sickness begin at 4–21 days (usual range 7–10 days) after initial exposure to the causative antigen. Symptoms and signs usually include fever, a cutaneous eruption (morbilliform or urticaria or the combination of these two reaction patterns) in >90% of patients, arthralgias in up to 50%, lymphadenopathy, and myalgias. Headache and gastrointestinal complaints may occasionally occur, as well. Less common manifestations include arthritis, nephritis, neuropathy, and other organ involvement.

The diagnosis is made on the basis of clinical findings, because there are no pathognomonic laboratory tests specific for the diagnosis of serum sickness or SSLRs in the acute setting. The erythrocyte sedimentation rate is noncontributory, because it may be elevated, normal, or low. Leukopenia or leukocytosis may be present, and serum sickness is one of the few illnesses in which plasmacytosis may be detected in the peripheral blood smear. The urine analysis may show proteinuria, hematuria, or hemoglobinuria. Serum creatinine and transaminases may be transiently elevated. Circulating immune complexes may rise and fall before symptoms and signs appear. Serum concentration of C3, C4, and total complement are depressed due to the formation of immune complexes, but they tend to rapidly return to normal.⁵⁷ Direct immunofluorescence microscopy of lesional skin from patients with serum sickness had demonstrated immunoreactants in seven of nine subjects, with immunoreactants being confined to the walls of dermal blood vessels and consisting of IgM, C3, IgE, and IgA. IgG was not identified in any of the specimens.⁵⁴

Therapy

Depending on the severity of the disease and its activity we, like others,⁵² recommend the administration of high-dose steroids for 3–5 days, followed by a prednisone taper. Typically, there is a noticeable improvement in the fevers and arthralgias within the first 48 hours of treatment, and resolution of symptoms is seen over approximately 8–10 days.⁵³ Some groups consider plasmapheresis the first-line therapy for serum sickness.^{58,59} Like others,⁵² however, we think that plasmapheresis should be reserved for steroid-resistant cases.

VASCULITIS

Vasculitis is inflammation of vessel walls. It has many causes, although they result in only a few histologic patterns of vascular inflammation. Vessels of any type in any organ can be affected, a fact that results in a wide variety of signs and symptoms. These manifold clinical manifestations, combined with the etiologic nonspecificity of the histologic lesions, complicate the diagnosis of specific forms of vasculitis. This is problematic, because different vasculitides with indistinguishable clinical presentations have very different etiologies, associations with specific diseases, involvement in certain organs, prognoses, and treatments. To make things even more complicated, there are many classifications and no agreed-upon diagnostic criteria for the various categories of vasculitis, particularly the small-vessel vasculitides.

Drugs cause approximately 10% of vasculitic skin lesions and should be considered in any patient with small-vessel vasculitis.^{60–62} Withdrawal of the offending agent alone is often sufficient to induce prompt resolution of clinical manifestations, obviating the need for systemic corticosteroids or more powerful forms of immunosuppression.

For more details on this topic, the readers are directed to another chapter in this book devoted entirely to purpura and vasculitis of any kind.

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Severe and acute complications of dermatologic therapies

Ronni Wolf, Jasna Lipozenčić, and Batya B. Davidovici

BACKGROUND

Although physicians from other specialties, like the population at large, still consider cutaneous maladies as being mainly esthetic, skin deep, and insignificant, they are generally aware that treatment of these diseases often requires a variety of potent systemic drugs and is not limited to topical therapy. These powerful medications may cause many adverse reactions, some of them severe, acute, and even life threatening.

*"There are no really 'safe' biologically active drugs. There are only 'safe' physicians."*¹ A "safe" physician must, most importantly, be well informed about adverse reactions at the time of prescribing a drug, during the follow-up period, and especially when one of these rare catastrophes suddenly occurs.

Because the diversity of severe adverse reactions to dermatologic therapies is almost endless, we have chosen to focus on new drugs and their less known adverse effects.

TARGETED IMMUNE MODULATORS (TIMS)/BIOLOGICS

Targeted immune modulators (TIMs)—commonly referred to as biological response modifiers or simply *biologics*—are a relatively new category of medications used in the treatment of certain types of immunologic and inflammatory diseases, including dermatologic diseases, most notably psoriasis.

Overall, TIMs appear to have a good tolerability profile, although some rare but acute serious adverse events, such as infections, hematologic reactions, neurologic events, infusion reactions, congestive heart failure, nephrotic syndrome, and others, are of concern.

Below is a listing of adverse events associated with TIMs.

Infusion Reactions

As is the case with any foreign protein-derived agent, infusion with chimeric antibodies that contain murine antibodies, such as infliximab (containing 25% murine proteins), can lead to infusion reactions, either acute or delayed. Overall, these reactions occur in up to 10%–20% of patients and usually during or within 2 hours after infusion,² and they can, in most cases, be easily managed.

Symptoms of acute infusion reaction include fever, chest pain/discomfort (e.g., tightening pressure), hypotension/hypertension, palpitations, urticaria, and hyperemia. Although such a reaction might very well be a harrowing experience to the uninformed, most of the symptoms diminish substantially or resolve completely after stopping the infusion or slowing its rate. The Division of Clinical Immunology Infusion Center at Mount Sinai Medical Center has developed a protocol for the treatment of initial severe acute reactions,^{3,4} which recommends stopping the infusion and starting an infusion of normal saline. The airway must be maintained, and oxygen

is given. Epinephrine (0.1–0.5 mL, 1:1000) is administered subcutaneously and can be repeated every 5 min for three doses. Intravenous (IV) hydrocortisone (100 mg) or IV methylprednisolone (20–24 mg) is also given, followed by IV diphenhydramine (25–50 mg) and oral acetaminophen 650 mg. Epinephrine and diphenhydramine have a rapid onset of action and, in cases of severe reactions, should be given before steroids, which have a slower onset of action.

Although those authors^{3,4} recommend restarting TIM infusion at a slower rate after resolution of the symptoms and that a "prophylaxis protocol" be followed for retreatment of patients who have experienced severe reactions, we believe there is no logical justification to do so, especially in view of the fact that we are treating a benign disease, and there are many other alternative medications from which to choose.

Infections

Following U.S. Food and Drug Administration (FDA) approval and the more widespread use of TIMs (particularly, anti-TNF- α for rheumatic and inflammatory bowel diseases), postmarketing surveillance data from the FDA MedWatch database have revealed a disturbing number of reports of serious infections in patients treated with these agents.⁵ The FDA has issued black box warnings about an increased risk of infections for all TNF- α inhibitors, stating that "Serious infections, including sepsis and pneumonia, have been reported in patients receiving TNF- α blocking agents. Some of these infections have been fatal."

The true incidence of infections and the effect of TNF- α blocking agents on these numbers cannot be ascertained with accuracy, particularly in view of the fact that rheumatologic patients have a higher risk for infection than do nonrheumatologic patients, and that they are also usually receiving other disease-modifying drugs that are associated with considerable risk of infections. We discuss several of the most significant infections reported so far, without entering into the issue of the quantitative effect of anti-TNFs to their incidence.

Tuberculosis (TB)

At the forefront of interest concerning serious infections and the use of TNF- α inhibitors are mycobacterial infections, particularly *Mycobacterium tuberculosis* (Mtb).

An estimated one-third of the world's population (outside the United States, where the disease is uncommon) has latent TB infection (LTBI), which can potentially progress to disease and further spread of the epidemic. In LTBI, the person has a small number of "latent" Mtb bacilli that are contained in granulomas in their bodies. These organisms are viable and are possibly in a slow state of replication. These bacilli will never cause disease in most infected persons, but the ones that do reactivate disease suffer considerable morbidity and mortality

and are also the major source of transmission of the disease, fueling the continued epidemic. Even though TB is usually not rapidly fatal, the disease may show a fulminant course in immunocompromised patients and may also have an atypical pattern and presentation. In a review of 70 TB cases associated with infliximab therapy where the FDA was notified,⁶ more than half of the patients had extrapulmonary TB (lymph-node disease, peritoneal disease, pleural disease, meningeal disease, etc.), and approximately one-quarter had disseminated TB. In contrast, among cases of TB in immunocompetent patients, approximately 18% were manifested as extrapulmonary disease, and disseminated disease accounted for less than 2%. TNFs have a central role in the host defense against Mtb. The human immune response is highly effective in controlling primary infection, resulting from exposure to Mtb.

TNF- α is involved in the killing of mycobacteria by activating macrophages and preventing the dissemination of infection by stimulating granuloma formation. Physicians should be aware of the increased risk of reactivation of TB among patients who are receiving anti-TNFs and, in particular, of the unusual clinical manifestations of the disease, of the high mortality rates in this group (12%)⁷ and of its sometimes fulminant course. Both infliximab and adalimumab have black box warnings on their product labels citing this risk.⁸

The Centers for Disease Control and Prevention (CDC) recommend TB screening with tuberculin skin test for all patients being treated with any TNF- α inhibitor. Although other biologic medications that are not anti-TNFs (such as alefacept or efalizumab) have not been reported to cause reactivation of latent TB infection, they are immunosuppressive, and the majority of advisors from the medical board of the National Psoriasis Foundation perform baseline TB testing before initiating therapy with either agent.⁸ Physicians should also bear in mind that a negative skin purified protein derivative (PPD) skin test and negative chest x-ray are not always reliable in patients with concomitant immunosuppression.⁹ Indeed, anergy to PPD testing has been reported to be as high as 50% in rheumatic arthritis patients, compared with 7% in controls.¹⁰ When active TB is suspected, treatment with TIMs should be immediately stopped until the diagnosis has been ruled out or the infection has been treated with antituberculosis agents. In addition, TB following therapy with anti-TNFs may be initially refractory to treatment due to lingering TNF- α blockers in the system.¹¹

Adherence to the guidelines caused a significant decrease in the rates of TB in a population of anti-TNF-treated patients. Most of the initial recommendations involve using PPD. Over the last few years, interferon gamma release assays (IGRAs) have increasingly been used to diagnose LTBI, and available data suggest that their performance is not inferior to PPDs. The benefits to using this test as a screening tool include ease of testing (i.e., no follow-up visit required, less subjectivity in interpreting results) and increased specificity in patients previously given Bacillus-Calmette-Guérin (BCG) vaccine. Except for the introduction of IGRAs, the current recommendations for screening and monitoring patients on biologics for TB have almost not changed over the last decade.^{12,13}

Listeria Infections

Listeria monocytogenes (*L. monocytogenes*) is a flagellated gram-positive bacterium that can cause life-threatening illness characterized by gastroenteritis, meningitis, encephalitis, and materno-fetal and perinatal infections. Infection with

L. monocytogenes is widespread in the environment; it is isolated from soil, vegetables, or animals; and it can be acquired as a food-borne infection through ingestion of contaminated food, such as unpasteurized dairy products, undercooked meats, and contaminated vegetables. *Listeria* cross the intestinal barrier by invading intestinal epithelial cells, reaching the liver and the spleen via the lymphoid system and blood circulation, where they are internalized by splenic and hepatic macrophages. During severe infections, the bacteria disseminate via the blood and cross the blood-brain barrier, resulting in infections of the meninges and the brain; furthermore, they can cross the fetoplacental barrier in pregnant women, which leads to infection of the fetus. *L. monocytogenes* is able to invade different nonphagocytic cells and is resistant to intracellular killing by macrophages after phagocytosis. *L. monocytogenes* predominantly affects pregnant women, immunocompromised patients, and older patients.

L. monocytogenes is controlled in infected tissue by immune defense mechanisms involving CD4+ and CD8+ T lymphocytes and TNF- α produced by macrophages, granulocytes, and dendritic cells. Immunosuppressive agents, including TNF- α inhibitors, increase the risk of opportunistic infections, among them systemic sepsis, meningoencephalitis, cholecystitis, and arthritis.¹⁴

The first case of *L. monocytogenes* infection complicating infliximab therapy was reported in 2000 in a patient with Crohn disease.¹⁵ *Listeria* infection in patients on anti-TNF- α treatment are summarized in a review¹⁶ published in 2013 of 43 cases of invasive *Listeria* infection associated with anti-TNF- α . Thirty-eight cases were related to infliximab, three to etanercept, and two to adalimumab. Three of the patients had psoriatic arthritis. Physicians should be aware of the possibility of this highly lethal infection in patients receiving anti-TNF- α treatments, because early recognition may help decrease morbidity and mortality.

Nocardiosis

Commonly found in soil, *Nocardia* spp. are gram-positive aerobic bacteria with a filamentous appearance similar to fungi. They are recognized as opportunistic pathogens and can be transmitted by inhalation. The infection may be localized cutaneous or lympho-cutaneous, or disseminated systemic, primarily involving the lung; however, they can also involve the central nervous system (CNS), cardiac, ocular, renal, and other systems, with untreated infections being associated with high morbidity and mortality.¹⁷ Even with appropriate treatment, the mortality rate for patients with either CNS or disseminated disease may be as high as 50%.¹⁸

TNF- α is essential for the formation and maintenance of granulomas, a key host defense against intracellular pathogens, including *Nocardia* infections.

Eight cases were identified in a literature search¹⁹ for cases of *Nocardia* infection in patients on anti-TNF- α . One of the patients had received medication for psoriasis, six had received infliximab, one had received etanercept and adalimumab, and one had received adalimumab.

A fatal case of disseminated *Nocardia* infection treated with infliximab and methylprednisolone for resistant Sweet syndrome has recently been reported.²⁰

Legionella Pneumonia

TNF- α has a major role in intracellular infection control and in granuloma maintenance. *Legionella pneumophila* is an

intracellular microorganism; therefore, TNF- α has a role in anti-*Legionella* defense. Consequently, patients receiving anti-TNF- α drugs are at increased risk for acquiring this infection.

The results of a prospective multicenter study of the incidence and risk factors of legionellosis in patients receiving anti-TNF- α drugs were reported in 2013.²¹ Twenty-seven patients with *Legionella* pneumonia who were receiving TNF- α blockers in France between 2004 and 2007 were evaluated. They had all been hospitalized, including nine (33.3%) in the intensive care unit (ICU). One patient died of legionellosis 4 days after diagnosis. The incidence for legionellosis was higher by 13-fold for patients receiving anti-TNF- α treatment than for the incidence for legionellosis measured for the global French population through mandatory notification. The high risk for legionellosis in patients receiving TNF- α antagonists was even higher in patients receiving monoclonal anti-TNF- α antibodies than in those receiving soluble receptor therapy. Those authors suggested that all patients with pneumonia who are receiving anti-TNF- α therapy should be tested for legionellosis with specific urine antigen detection. They also suggested that “the first-line antibiotic therapy for pneumonia in patients receiving anti-TNF- α therapy should be active against *Legionella pneumophila*.”

Visceral Leishmaniasis

Visceral leishmaniasis (VL) may represent a rare complication of biologic therapies. An effective leishmania-specific Th1-response renders the dermal inoculation of flagellated parasites of *Leishmania* clinically asymptomatic or subclinical in most immunocompetent subjects.

In a recent literature search²² for patients on anti-TNF- α who developed VL, a Brazilian group found 28 published cases and added 4 cases of their own. All reported cases came from endemic areas. The infection was detected on an average of 23.5 months after the initiation of anti-TNF therapy. The majority of cases had classic clinical presentations. Obviously, questions about the possibility of distinguishing cases of new parasite infestation from those caused by reactivation of a latent infection usually cannot be answered; however, it is more important to raise the index of suspicion for this rare infection in patients on anti-TNF therapy, and thereby possibly facilitate early diagnosis for these patients.

Histoplasmosis and Other Fungal Infections

Host responses to pulmonary inoculation with fungus *Histoplasma capsulatum* are similar to pulmonary mycobacterial infection. Histoplasmosis is the most prevalent endemic mycosis in the United States, and approximately 250,000 individuals are infected per year. As with TB, 90%–95% of exposed immunocompetent hosts will develop latent asymptomatic disease, but reactivation and dissemination, which can be severe and fatal, may occur in the context of therapy with immunosuppressants.²³

A total of 281 cases of invasive fungal infections (IFI) associated with TNF- α inhibitors were found in a literature search from 2008.²⁴ Of these, 226 (80%) were associated with infliximab, 44 (16%) with etanercept, and 11 (4%) with adalimumab. The most prevalent IFIs were histoplasmosis (30%), candidosis (23%), aspergillosis (23%), and coccidioidomycosis (10%). Pneumonia was the most common pattern of infection. Of the 90 (32%) of 281 cases for which outcome information was available, 29 fatalities (32%) were recorded.

Histoplasmosis is the most commonly reported invasive fungal infection in patients treated with TNF- α inhibitors, and it is found three times more frequently in these patients than is TB. The incidence is estimated at 18.8 per 100,000 persons for infliximab and 2.7 per 100,000 persons for etanercept, with a mortality rate of 20%.²⁵ As with other infections, it cannot be established whether histoplasmosis develops secondary to a newly acquired infection or from reactivation of a latent disease.

Pneumocystis carinii pneumonia (PCP) is a common opportunistic infection in immunocompromised persons. There have been 44 reported cases of PCP in the United States following the use of infliximab, and five cases of PCP following etanercept, with six fatal cases among them.²⁶

A search of the FDA Adverse Event Reporting System for cases of PCP associated with infliximab use revealed 84 cases. Most of the patients received concomitant immunosuppressive medications. Twenty-three of those 84 (27%) patients died.²⁷ Although from 2007, this is the most recent case series.

In summary, disseminated fungal infections should be carefully considered in the differential diagnosis of patients who present to the emergency room or intensive care setting with a serious febrile illness in the setting of anti-TNF therapy, especially in areas of high disease prevalence.

Congestive Heart Failure (CHF)

Worsening or exacerbation of CHF is inarguably a serious, life-threatening and frightening adverse effect. The question is, to what extent, if at all, are TNF- α antagonists involved in this event?

It is known that worsening CHF has been associated with elevated serum levels of TNF- α . Initial data from animal models and from preclinical and pilot studies were encouraging, showing some anecdotal efficacy of TNF- α antagonist therapy in the treatment of CHF.^{28,29} Two larger, multicenter, randomized, placebo-controlled clinical trials (i.e., RECOVER [Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction] and RENAISSANCE [Randomized Etanercept North American Strategy to Study Antagonism of Cytokines]) failed to show any significant difference in composite clinical function score for anti-TNF- α therapy versus placebo. Both studies were terminated early, because interim analysis did not show any benefit of etanercept on morbidity or mortality. For the RENAISSANCE study, the key finding was a trend toward higher mortality in etanercept-treated subjects, a concern heightened by the apparent dose-response relation.^{28,29} A phase II trial with infliximab indicated a strong trend toward an increase in the percentage of patients with worsening clinical status with increasing infliximab dose, largely due to an increase in deaths or hospitalization for CHF at weeks 14 (primary endpoint) and 28.³⁰

In an examination of case reports³¹ of all patients who developed new or worsening CHF while receiving TNF- α antagonist therapy, investigators obtained a total of 47 reported cases from the FDA's MedWatch system. After receiving TNF- α antagonist therapy, 38 patients developed new-onset CHF, and nine patients experienced CHF exacerbation. Of the 38 patients with new-onset CHF, 19 (50%) had no identifiable risk factor, and 10 patients were younger than 50 years. After TNF- α antagonist therapy was discontinued and heart failure therapy was started in these 10 patients, three had complete resolution of heart failure, six improved, and one died, an outcome that supports a causal relationship between TNF- α therapy and CHF.

In a recent study³² that evaluated long-term efficacy and safety of ustekinumab, 0.48 cases of major adverse cardiovascular events (MACEs) per 100 patient-years of follow-up through week 261 (year 5) were recorded.

A 2014 review³³ of the literature from the Medical Board of the National Psoriasis Foundation aimed to define the impact of common psoriasis therapies on cardiovascular measures and outcomes. Infliximab therapy for CHF was shown to increase hospitalizations, morbidity, and mortality and is contraindicated in moderate to severe CHF, whereas etanercept did not demonstrate these effects. In one metaanalysis³⁴ cited in this review, the rate of CHF was not significantly different between the patients who received biologics and the nontreated controls. The association of MACE (defined in that work as MI, cerebrovascular accident, or cardiovascular death) was evaluated in another metaanalysis³⁵ of controlled trials on ustekinumab or briakinumab. Although 10 MACEs occurred in 3179 patients treated with IL-12/23 inhibitors and none occurred in 1474 placebo-treated patients, there was no significant increase in the risk of MACE. Other studies^{36,37} demonstrated similar findings.

There are currently no concrete guidelines for the evaluation and treatment of patients with suspected CHF. It is generally agreed upon that infliximab >5 mg/kg is contraindicated in patients with severe CHF; likewise, patients who develop new-onset CHF while on anti-TNF therapy should immediately stop medication, undergo a prompt evaluation, and receive appropriate treatment. We currently advise against the reinstitution of anti-TNF therapy in such patients with dermatologic diseases. As for patients with well-compensated mild CHF, each patient's risk versus benefit should be considered before therapy is begun.

Serious Neurologic Events

Seizure Disorder

Seizure disorder following anti-TNF therapy is rare, having been reported in 29/170,000 patients who had been exposed to infliximab, in 26/104,000 exposed to etanercept, and in none exposed to adalimumab.^{26,38} In view of these data, preexisting seizure disorder does not seem to be a contraindication to anti-TNF therapy for rheumatoid arthritis patients.^{26,38} We, however, think that dermatologic patients should have an alternative therapy.

Demyelination

As is the case for TNF- α antagonists and CHF, the fact that patients with multiple sclerosis (MS) show elevated TNF- α levels in serum and cerebrospinal fluid (CSF) prompted researchers to try this form of therapy for patients with MS. To this end, a TNF- α blocker named lenercept, which was developed and studied *specifically* for patients with MS (not for dermatologic or rheumatologic patients), resulted in an increase in MS exacerbations and a shortened time to flare.³⁹ An open-label, phase I safety study of infliximab carried out on two patients with MS showed a worsening of the disease.⁴⁰

Demyelinating disorders have been described in postmarketing surveillance and in published case reports for all three TNF- α blockers.^{26,38,41} The incidence of demyelinating disease, however, does not appear to be increased in patients on anti-TNF therapy compared with the background rate in the general population^{26,38,41}; nonetheless, these agents should be avoided in patients with preexisting demyelinating conditions until more data are available on the relationship between TNF- α blocker

and demyelination.^{26,38,41} In this context, physicians should be aware of the signs and symptoms of demyelinating diseases, including weakness, paresthesias, visual disturbances, confusion, and gait disturbances. Obviously, therapy with TNF- α inhibitors should be immediately stopped if a patient develops any suspicious neurologic signs, and neurologic consultation obtained.

Guillain-Barré Syndrome (GBS) and Miller Fisher Syndrome (MFS)

A 2013 literature search⁴² presented data on 23 patients with GBS, who were taking anti-TNF- α drugs. Twenty-one had GBS and two had MFS. Of the 14 cases where sufficient information was provided, 10 corresponded to a demyelinating GBS and 4 to the axonal variant. When the GBS appeared, 11 patients were on treatment with infliximab, 5 with etanercept, and 7 with adalimumab, probably more or less reflecting the number of patients in that study cohort who were treated with each of the drugs. In some cases, more than one anti-TNF- α drug had been used.

Some recent reports have raised doubts about this apparent increase in GBS in patients treated with anti-TNF- α drug. In a study conducted on patients with rheumatoid arthritis (RA), those treated with anti-TNF- α had a lower risk of developing demyelinating events. The adjusted rate ratio in individuals not at high risk was 1.31 (95% confidence interval [CI] 0.68 to 2.50) after exposure to anti-TNF agents and 0.80 (95% CI 0.29 to 2.24) after exposure to anakinra. Those authors attributed this lower incidence of demyelinating events to the tendency not to use these drugs in patients with a history of these diseases.⁴³

Serious Hematologic Events

Although extremely rare, serious and acute hematologic dyscrasias, such as aplastic anemia and pancytopenia, have been described in association with the use of TNF- α inhibitors. There are no current recommendations for regular monitoring of blood counts, but physicians should be aware of the possibility of hematologic adverse events. If one occurs, TNF blockers should be stopped, and the patient should be checked for evidence of other underlying disease or other causative medications before ascribing the event as potentially related to the TNF blockade.^{26,38,44}

Efalizumab, an immunosuppressive recombinant humanized IgG1 kappa isotype monoclonal antibody that binds to human CD11a, is another biologic therapy utilized in the treatment of psoriasis.

Four cases of hemolytic anemia have been reported with efalizumab. Two cases found during clinical trials required discontinuation of therapy and blood transfusions. There is no descriptive information about the other two cases. A precaution regarding immune-mediated hemolytic anemia was added to the package insert for efalizumab.^{45,46} Eight cases of thrombocytopenia (0.3%) were reported in a combined safety database of 2762 patients who received it, all eight being consistent with an immune-mediated process. Three individuals were asymptomatic, and three required hospitalization, including one with heavy uterine bleeding. Five of the eight patients were treated with systemic steroids. Postmarketing cases of thrombocytopenia have also been reported. Prescribing information for efalizumab advocates monitoring for signs and symptoms of thrombocytopenia along with obtaining baseline

and periodic assessments of platelet counts.^{45,46} The reporting of one case of efalizumab-induced autoimmune pancytopenia has resulted in the recommendation of close monitoring of all blood cell counts.⁴⁵

Miscellaneous

Vasculitis

Rare cases of vasculitis associated with anti-TNF therapy have been reported, some of them severe. The causal relationship between the drug and the vasculitis remains uncertain, however, because the possibility of rheumatoid vasculitis cannot be excluded.^{47,48}

Hepatotoxicity

Although TNF- α inhibitors have no confirmed liver toxicity, rare cases of serious liver disease, suspected of having been induced by these drugs, have been reported.^{49,50}

Autoantibodies and Drug-Induced Lupus

TNF- α inhibitors can lead to the formation and increased titers of autoantibodies and antinuclear antibodies. The formation of these antibodies is not associated with any specific clinical findings. A SLE-like syndrome occurs rarely (approximately 0.2%) and seems to be associated with TNF- α inhibitors. The outcome of the disease had been favorable, with the disease being reversible upon cessation of the drug. No patient thus far has reportedly developed neurologic or renal disease.^{26,41}

RITUXIMAB

Although rituximab actually belongs to TIMs, we decided to deal with it separately. Rituximab (RTX) is a chimeric murine-human monoclonal therapeutic antibody against the CD20 antigen of B lymphocytes that was approved by the FDA in 1977 for the treatment of lymphoma⁵¹ and in 2006 for the treatment of RA.⁵² Initially used in the treatment of non-Hodgkin B-cell lymphoma, the scope of RTX has been expanded to include autoimmune diseases, such as RA, systemic lupus erythematosus (SLE), and chronic immune thrombocytopenic purpura syndrome. Over the last decade RTX has been used off-label to treat various autoimmune blistering diseases,^{53,54} including pemphigus vulgaris (PV),^{55,56} bullous pemphigoid (BP),^{55,57} mucous membrane pemphigoid (MMP),^{55,58} ocular cicatricial pemphigoid (OCP), and epidermolysis bullosa acquisita (EBA).^{54,55}

The current data on the use of RTX in the treatment of autoimmune mucocutaneous blistering diseases (AMBDs) were evaluated in a recent review⁵³ that described the life-threatening complication of this treatment when used in dermatologic diseases. RTX was used to treat PV in 475 patients, and serious adverse events (SAEs) were reported in approximately 4% of them. Approximately 79% of the SAEs were due to infections, most of which required hospitalization. Half of these infections resulted in septicemia. Thrombotic events were reported in two patients, and late-onset neutropenia was documented in one patient. That literature search identified 16 patients with BP treated with RTX, and three of them died, reportedly due to bacterial sepsis and cardiac complications. The majority of patients diagnosed with BP were elderly and had previously been treated with corticosteroids and other immunosuppressive drugs. Forty patients with MMP treated with RTX were evaluated in the same review. One patient died, and there were two SAEs: one patient developed severe pyelonephritis and

the other died from tuberculosis. Both had hypogammaglobulinemia at the time of death. Sixteen patients with EBA treated with RTX were identified, all of whom had mucocutaneous disease. One patient died due to PCP.

The mortality associated with RTX use in autoimmune diseases was assessed in an earlier analysis by the same authors.⁵⁹ Fatal outcomes were recorded in 14 patients with AMBD out of 134 patients evaluated (10.4%). The causes of death were infections (75%), gastrointestinal complications (17%), and cardiac events (8%). In evaluating the mortality rate in a very large cohort (4320 patients) with autoimmune diseases other than AMBD who were treated with RTX, there were 101 deaths, yielding a mortality rate of 2.4%. As such, there is a significantly higher mortality rate in AMBD patients compared to patients with other autoimmune diseases. The cause of death was attributed to infection (43.6%) and to cardiovascular (15.8%), pulmonary (5.5%), malignant (6%), hematologic (6%), and gastrointestinal causes, as well as to progression of disease.

In a European phase II study of rituximab for 131 patients with newly diagnosed hematologic malignancies, eight patients (6%) did not finish therapy due to adverse events, such as anaphylaxis/severe allergic reaction ($n = 3$), elevation in serum liver function tests ($n = 1$), syncope ($n = 1$), syncope and bradycardia ($n = 1$), and urticaria and hypotension ($n = 1$).⁶⁰

Cardiovascular toxicity in the form of cardiac dysrhythmias has been reported in 8% of patients treated with rituximab. These include monomorphic ventricular tachycardia, supraventricular tachycardia, trigeminy and irregular pulse, and an isolated case of a fatal infusion secondary to myocardial infarction (reviewed in Ng et al.⁶¹).

Progressive Multifocal Leukoencephalopathy (PML)

PML is a rare demyelinating disease of the CNS that results from reactivation of latent John Cunningham (JC) polyoma virus (JCV) and is associated with a high rate of morbidity and mortality. Up to 92% of the adult population is JCV-seropositive. Reactivation of the virus typically occurs in persons with suppressed cellular immunity, particularly those with HIV infection, hematologic malignancies, transplant patients, and patients who are otherwise immunosuppressed (reviewed in Carson et al.⁶²). A 2009 review of the literature⁶² identified 57 PML cases occurring among HIV-negative patients treated with rituximab. All 57 patients had received prior therapies that are known to affect immune function, including alkylating agents and corticosteroids. The case-fatality rate was 90%.

Figures published in 2014 revealed that more than 70 cases of PML have been associated with the use of rituximab, predominantly in patients treated with lymphoproliferative disorders.⁶³

METHOTREXATE (MTX)

Since the mid-1950s, methotrexate (MTX) has become the gold standard by which other systemic psoriasis medications are measured.⁶⁴ MTX has been safely prescribed to thousands of patients with psoriatic and rheumatoid conditions with great therapeutic benefit. The fact that 58% of surveyed dermatologists used MTX to treat patients with severe psoriasis in 1987⁶⁵ indicates that dermatologists feel comfortable with this form of therapy. A significant number of dermatologists are, however, still unwilling to treat psoriasis with MTX, reflecting a

persistent bias against it. The good benefit/toxicity ratio, low cost, extensive experience over decades, and relatively good tolerability of MTX notwithstanding, it is, like the majority of cancer medications, a toxin and an antimetabolite and, as such, it can cause acute toxicity. In this chapter we focus on some acute, serious adverse reactions of MTX.

Pancytopenia

Bone marrow toxicity, specifically, pancytopenia, is the most serious, acute, and, therefore, frightening side effect of MTX, with an estimated incidence of 1.4%.⁶⁶ MTX-induced bone marrow suppression develops suddenly, rapidly, and without warning signs. It seems unlikely, therefore, that a more frequent monitoring schedule would substantially avoid its occurrence. Although it usually occurs late into treatment,⁶⁷ there are several reports on early occurrence, even after one or two doses of MTX.^{66,68} The outcome is grave, with a reported mortality rate ranging from 17%⁶⁶ to as high as 44%,⁶⁸ most commonly resulting from infections and bleeding disorders.

Physicians should be alerted to this potentially life-threatening complication, if not to avoid it, then at least to recognize this adverse event, as early as possible, and to take the appropriate measures.

Pulmonary Complications

Although the major safety concern of MTX is its hepatotoxicity, it is less known that pulmonary toxicity is only slightly less common and not less serious: it is the reason for withdrawal of MTX in 1 in 108 patient-years compared with 1 in 35 patient-years for hepatic toxicity. The prevalence of MTX-induced pneumonitis is reported to be 0.3%–7.5%,⁶⁹ and more than 120 cases have been reported in the English-language literature since its first description in 1969.⁶⁹ Pneumonitis following MTX is a serious, potentially fatal hypersensitivity reaction and is far less predictable than hepatic and hematologic toxicity. A review of 123 published cases of MTX-induced pneumonitis showed a mortality rate of 13%.⁶⁹ Although most patients with MTX pneumonitis have the subacute type with progression over several weeks, a life-threatening, acute type with rapid progression over only a few days has also been reported.^{69,70} Differentiation between MTX pneumonitis and acute respiratory infection is not always easy, in spite of the accepted diagnostic criteria.⁷¹ A suggested management approach^{69,70} for a patient with suspected MTX-related lung pathology consists of MTX discontinuation, supportive therapy, and most importantly, a comprehensive diagnostic procedure to exclude infection. It should consist of extensive cultures of sputum, blood, and bronchoalveolar lavage (BAL) fluid, and serologic testing for common respiratory viruses, mycoplasma, rickettsiae, and legionella. Microscopic examination of BAL fluid is recommended to exclude *Pneumocystis carinii*, fungi, and mycobacteria. Because excluding infection might sometimes be difficult and time consuming in cases where rapid treatment is required, empirical antimicrobial treatment and, in some cases, intravenous corticosteroids should be initiated, until there is evidence of clinical and radiologic improvement.

CYCLOSPORINE A (CYCLOSPORINE A)

Cyclosporine (CsA) has a range of side effects that are the subject of much concern. It may seem surprising that this drug is

generally very well tolerated and, ironically, the good tolerability itself can represent a hazard, because patients are not likely to be aware of any signs of its chronic toxicity.

Nephrotoxicity and Hypertension

The major safety concerns of CsA are nephrotoxicity, hypertension, and the potential risk of malignancy. There are three different forms of CsA nephrotoxicity: reversible acute renal dysfunction, hemolytic-uremic-like syndrome, and irreversible chronic nephrotoxicity:

1. CsA-induced acute nephrotoxicity is a hemodynamically mediated phenomenon, characterized by the absence of permanent structural changes and by reversibility with decrease or discontinuation of the drug. It is a dose-related, clinically asymptomatic increase in serum creatinine, which can occur even when drug blood levels are in the therapeutic range. In such patients, renal histology is usually normal or shows only nonspecific changes, like vacuolization or the presence of giant mitochondria in tubular cells.⁷²
2. Recurrent or *de novo* hemolytic-uremic syndrome is rare, generally multifactorial, and very seldom related exclusively to CsA.^{72,73} It occurs mainly in bone marrow and solid organ transplanted patients and has not been reported in patients on CsA therapy for dermatologic diseases.⁷⁴
3. Chronic CsA nephrotoxicity is an insidious condition associated with an irreversible and progressive renal interstitial fibrosis, followed by important decrease in renal function.⁷² It is related to long-term exposure to CsA and is never an acute event.

Neurotoxicity

Observation of acute neurotoxicity in conjunction with high concentrations of CsA in blood was reported soon after CsA's introduction into clinical practice in 1979.⁷⁵ Subsequently, severe neurotoxicity resulting from CsA treatment has been frequently reported not only in bone marrow and solid organ recipients, but also in patients with dermatologic⁷⁶ or autoimmune diseases.⁷⁷ Neurotoxicity had been less well-known, but with growing experience, central nervous system side effects are now reported in up to 40% of patients treated with CsA.^{78–80} The most commonly noted neurologic finding is tremor, appearing in 20%–40% of patients treated with the drug.^{78,79} This side effect is not particularly distressing for most patients and tends to diminish with time. Visual hallucinations are less frequently reported, and cortical blindness is extremely rare and reversible in most (although not all) of the patients.⁷⁹ A mild encephalopathy due to CsA has been found in up to 30% of patients, and cessation or reduction in dose is usually followed by relief of symptoms.^{78,79} Severe encephalopathy, altered level of consciousness, psychosis, and coma have all been reported.^{78,79}

Seizures were reported to occur in 1.5%–6% of CsA treated patients. Most patients suffered a single seizure, without recurrence after dose reduction, although rare cases with status epilepticus have been reported.⁷⁸

In summary, CsA induces neurologic side effects in up to 40% of patients. The clinical manifestations can be mild (e.g., tremor, headache, and neuralgia), moderate (e.g., visual disturbances and cortical blindness), or severe (affecting up to 5% of patients; e.g., altered level of consciousness, confusion, seizures, and coma). These side effects are almost always

reversible upon reduction or cessation of treatment; however, permanent changes have also been reported.

RETINOIDS (ISOTRETINOIN)

Isotretinoin (13-*cis*-retinoic acid) is a synthetic oral retinoid that has high efficacy against severe, recalcitrant, and nodulocystic acne.

Isotretinoin, a vitamin A derivative, interacts with many of the biologic systems of the body and, as such, has a diverse pattern of adverse effects, not unlike that seen in hypervitaminosis A. The side effects involve the mucocutaneous, musculoskeletal, metabolic, gastrointestinal, hepatobiliary, ophthalmic, and central nervous systems, including headaches. Most of the adverse effects are mild and temporary, resolving after the drug is discontinued: some rare complications persist, and these will be discussed.

In a retrospective analysis of 1193 suspected pediatric adverse drug reactions (ADRs) reported to Health Canada (1998–2002),⁸¹ 41 reports included a fatal outcome of which isotretinoin was responsible for two, making it second (together with six other drugs) to olanzapine, with three fatal cases. Of 14 cases that were defined “recovered with sequelae,” isotretinoin with three cases was alone in first place.

Psychiatric Disorders

Grave side effects attributed to isotretinoin are depression, psychosis, suicide, and suicide attempts. On February 25, 1998, the FDA mandated a change in the label warning to include, “Psychiatric disorders: Accutane may cause depression, psychosis and rarely, suicide ideation, suicide attempt and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary.”⁸² This warning notwithstanding, the issue is still not entirely clear, and studies (mostly sponsored) conclude that the existing reports do not meet the required criteria for establishing causality between the ingestion of isotretinoin and suicide or major depression and that the risk of depressed mood is no greater during isotretinoin therapy than during other therapy of an age-matched acne group. The link between psychiatric disorders and isotretinoin remains a controversial issue.^{82–85}

Intracranial Hypertension

Severe headache is the most frequently reported adverse effect of isotretinoin.^{86,87} About one-fourth of the cases are due to pseudotumor cerebri. Although this side effect is almost always reversible and leaves no sequelae, it can have a devastating outcome (there are cases of irreversible blindness, personal communication) if not recognized early enough and treated appropriately.

Ocular Side Effects

These are very common although rarely serious. There have been a number of cases of optic neuritis, cortical blindness, corneal ulcers, and glaucoma that were possibly associated with isotretinoin.⁸⁸

Gastrointestinal, Hepatobiliary

Gastrointestinal, together with hepatobiliary side effects, are the second most commonly reported adverse reactions after psychiatric disorders.⁸¹

Although inflammatory bowel disease (IBD) is described as a possible adverse drug reaction in the product information of isotretinoin, this association has been given little attention in the literature. There are many cases of IBD reported to the FDA and the World Health Organization (WHO) (101 reports on isotretinoin with ulcerative colitis and 35 reports on isotretinoin with Crohn disease), and cases of IBD are significantly more often reported in association with isotretinoin than with other drugs, thus supporting an association between the drug and the condition.⁸⁹

Derangements of lipid metabolism leading to increased triglyceride and cholesterol levels are well-known side effects of retinoid therapy and are usually harmless, although the rare cases of marked hyperlipidemia associated with pancreatitis are always serious and of major concern.^{85,90,91}

INTRAVENOUS IMMUNOGLOBULIN (IVIG)

IVIG is a blood product consisting primarily of intact IgG molecules, which is derived from pooled normal human plasma of between 1000 and 15,000 donors per batch. Its dermatologic uses are for Kawasaki disease, therapy-resistant dermatomyositis, toxic epidermal necrolysis, and the blistering diseases, particularly pemphigus. Examples of conditions for which the evidence consists mainly of case series or reports include atopic dermatitis, chronic urticaria, scleromyxedema, and erythema multiforme.

Several serious, acute, and potentially fatal adverse effects are known to be associated with IVIG therapy. Fortunately, these side effects are rare.

Acute Renal Failure

One of the most significant concerns of IVIG therapy is its association with acute renal failure. Interestingly, it is not the immunoglobulins that mostly cause renal insufficiency, but the sugar that is added to some of the products to stabilize the solution and minimize aggregate formation. Up to 90% of the IVIG-associated renal adverse events have been linked to sucrose-containing preparations.^{92,93} The mechanism involved is osmotic nephrosis. Sucrose is a disaccharide that is enzymatically cleaved into glucose and fructose, when it is ingested orally; however, the cleaving enzyme is not present in the blood or kidney. When given intravenously, the sucrose molecule remains intact and is excreted through the kidney. During this process, the sucrose is taken up (pinocytosed) into the proximal tubular cells, causing an osmotic gradient and leading to the entrance of fluid into the cells and to cell damage (“osmotic nephrosis”).

Cerebral Vascular Accident (CVA)

A CVA is a rare but potentially fatal side effect of IVIG therapy. One review of a series of 16 cases⁹⁴ and an additional 13 case reports⁹⁵ provided the clinical features of this unusual occurrence. Most patients had received an IVIG dose of 2 g/kg/cycle. All of them had received IVIG at the recommended infusion rate or slower. Most patients developed stroke within 24 h of completing an infusion, indicating a direct temporal relationship to the administration of IVIG. Slightly more than one-half of the patients were receiving their first cycle of IVIG, suggesting that factors intrinsic to certain patients may have put them at higher risk for stroke than others. Common risk factors for a CVA were present in most of the patients.

Currently, there is no clear understanding of the pertinent pathophysiology of this serious and sometimes fatal side effect. As a result, there are no recommendations for prophylaxis and treatment. The only suggestion we can offer is that all patients who are being evaluated for potential IVIG therapy need to be questioned about known risk factors for a CVA. The risk-to-benefit ratio of using IVIG in these patients should be discussed with patients and family members.⁹⁵

Arterial and Venous Thrombotic Complications Including Myocardial Infarction

One series and review of literature analyzing this complication has been published in a dermatologic journal.⁹⁶ This series demonstrates that IVIG-related thrombotic arterial/venous complications are not uncommon in patients with autoimmune disorders (six [13%] out of 46 patients developed IVIG-related thrombotic complications). Thrombotic complications frequently occurred during IVIG infusion (50%), although they were also observed within 1–8 days following IVIG infusion in other patients. Three of six patients developed deep venous thrombosis or pulmonary embolism, two developed myocardial infarction, and one suffered a stroke. Although the outcome of the thrombotic complications was favorable in all their patients, the authors' literature review indicates a serious outcome with a mortality rate of 20%–30%.⁹⁶ In addition, 15% of the patients died of IVIG-associated thrombosis.

In another large series of 279 IVIG-treated patients,⁹⁷ five (4.7%) developed acute myocardial infarction during or shortly (3–5 h) after infusion. These cases occurred only with the use of one brand (Polygam).

As with other complications of this therapy, there are no specific recommendations, except for reweighing the risk-benefit ratio, close monitoring, infusion at a slow rate, and, if possible, administration of not too high doses after good hydration in patients with underlying predisposing factors. No consensus has been reached on the use of prophylactic antiplatelets or anticoagulants.

Aseptic Meningitis

Aseptic meningitis may be defined as inflammation of the meninges that clinically presents with headache, nausea, vomiting, fever, photophobia, painful eye movements, and nuchal rigidity. Drug-induced aseptic meningitis (DIAS) is usually benign, the clinical course is short-lived, and there is spontaneous resolution of the clinical manifestations without sequelae within hours to days after discontinuation of therapy. No deaths were reported in association with this syndrome.^{98,99}

The main challenge for the clinician is, however, the diagnosis. The differential diagnosis of DIAS is broad and includes infectious causes. Bacterial meningitis has similar, if not identical, signs as DIAS, and these two entities cannot be distinguished on clinical grounds. Bacterial culture of the CSF may help in the diagnosis. Treatment with third-generation cephalosporins has been suggested in cases where the presence of bacterial meningitis is a possibility.⁹⁸ Viral aseptic meningitis is another important consideration in terms of frequency, although less critical in terms of prognosis and management. Finally, other noninfectious causes of aseptic meningitis should be considered, such as SLE aseptic meningitis, as well as other drugs that can cause the syndrome. Intracranial bleeding, especially in patients with idiopathic thrombocytopenic purpura and bleeding disorders,

must also be considered. Computed tomographic scans should be used to rule out hemorrhage.

CONCLUSIONS

Dermatologists have the good fortune to work on the most accessible organ of the body. This gives them numerous advantages, and greatly facilitates not only the diagnosis but also the treatment of the skin disease, because many inflammatory and neoplastic conditions can be effectively managed, using a wide range of externally applied modalities. All this notwithstanding, many serious, widespread, and life-threatening dermatoses often need to be treated with potent systemic therapies. Because systemic drugs are increasingly available and are very often essential and indispensable for the treatment of dermatologic diseases, drug toxicity and adverse events are a significant problem. In view of the continuing development of new and effective therapies, it is expected that their incidence will not decrease. This book is mostly devoted to the treatment of serious dermatologic diseases, but this chapter deals with the other side of the coin, namely the adverse effects, consequences, and risks of our treatments.

This chapter has identified five major drugs or drug groups (biologics, methotrexate, cyclosporine A, retinoids, and IVIG) used in dermatology that are associated with an element of risk in causing serious and sometimes fatal adverse reactions. Basic principles of diagnosing, monitoring, and treating these adverse effects have been presented.

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Severe and acute allergic and immunologic reactions I: Urticaria, angioedema, mastocytosis, and anaphylaxis

Samuel H. Allen

BACKGROUND

Local wheals (synonyms: “nettle rash,” hives) and erythema that resemble the effect of the common stinging nettle (*Urtica dioica*) on the skin is known as urticaria. The edema involves superficial skin to the mid-dermis. Pruritus is common.

Angioedema (synonyms: angioneurotic edema, Quincke edema) produces a similar eruption but with larger edematous areas that affect both the dermal and subcutaneous and/or submucosal tissues. Angioedema is usually painful rather than itchy and is less well defined or normal in color. Both types of reaction can be triggered by drug allergies, insect stings, bites or contact, desensitization injections, cold temperature, other physical stimuli, or ingestion of certain foods, particularly eggs, shellfish, nuts, or fruits.

Mastocytosis is caused by an abnormal conglomeration of mast cells at a particular site. Degranulation, through rubbing or contact, triggers release of excessive histamine, resulting in localized swelling.

Anaphylaxis represents an extreme form of acute allergic reaction that is mediated by immunoglobulin E (IgE). Anaphylaxis is an example of a type I hypersensitivity reaction (see Chapter 19). Although erythema, urticaria, and angioedema may all occur, it is the systemic hypotension and shock that determine the outcome. Anaphylaxis is a clinical emergency that is characterized by profound shock that may rapidly lead to cardiorespiratory arrest. A similar picture from nonallergic causes is called an “anaphylactoid reaction.”

URTICARIA

Urticaria (see Figure 18.1) may result from different stimuli on an immunologic or nonimmunologic basis. The most common immunologic mechanisms are hypersensitivity mediated by IgE and activation of the complement cascade.

The physical urticarias, which account for approximately 25% of cases, include dermatographism and the pressure, cold, heat, solar, cholinergic, and aquagenic urticarias (Table 18.1). The trigger may not always be identified, even when such reactions are recurrent. This can be frustrating to the patient and the dermatologist alike. Urticaria may accompany, or even be the first symptom of, severe viral infection including hepatitis, infectious mononucleosis, and rubella. Similar lesions may precede, or be associated with, an underlying vasculitis (urticarial vasculitis), malignancy, pemphigoid, or dermatitis herpetiformis, the cutaneous manifestation of celiac disease.

Dermatographism is a wheal-and-flare reaction seen after scratching or stroking the skin firmly with a hard object and is caused by an exaggerated release of histamine. Pressure urticaria is caused by sustained pressure from tight clothing, hard seats,

and stiff footwear and may present as an immediate or late (4–6 hours, occasionally 24 hours) reaction to the pressure stimulus. Cold urticaria varies in severity and is induced by cold wind or bathing in cold water. Bronchospasm and histamine-mediated shock occur in extreme cases and may result in drowning. In its rare familial form, it appears in infancy.

Warm environments often exacerbate the physical urticarias, but pure heat urticaria is rare. Solar urticaria is likewise a rare condition, in which ultraviolet rays from sunlight cause an urticarial eruption. Aquagenic urticaria is independent of temperature and occurs on skin contact with water. Cholinergic urticaria appears to be caused by an unusual sensitivity to acetylcholine and is characterized by small, highly pruritic, discrete wheals, surrounded by a large penumbra of erythema that occur after exertion, stress, or heat exposure. A skin challenge test using methacholine 1:5000 may reproduce the lesions in about one-third of cases. A more reliable diagnostic method is to induce the urticarial reaction by exercising the subject with an occlusive dressing to promote sweating.

Chronic urticaria and angioedema with symptoms lasting more than 6 weeks are more difficult to explain; only rarely can a specific cause be found.¹ Some patients with chronic urticaria demonstrate autoantibodies directed against mast-cell epitopes with histamine-releasing activity, but these are the exception. Occasionally, chronic ingestion of an unsuspected drug or chemical is responsible (e.g., from antibiotics used in animal husbandry that may be present in small quantities in meat for human consumption; from use of nonprescription drugs; or from preservatives, dyes, or other food additives) (Table 18.2).

Despite anecdotal reports of urticaria occurring with lymphoma and systemic malignancy, no association was found in a large epidemiological study.² In contrast, a higher frequency of autoimmune disease is found among patients with ordinary urticaria.³

ANGIOEDEMA

A familial form of urticaria was described by John Milton (1820–1898) and termed “hereditary angioedema” in 1876.⁴ It is transmitted as an autosomal dominant trait and thus affects successive generations. The term “angioneurotic edema” was introduced a few years later, as it was believed that mental stress could precipitate attacks.⁵ Hereditary angioedema is now known to be associated with a deficiency in serum inhibitor of the activated first component of complement.⁶

The genetic defect has been mapped to chromosome 11. More than 100 different mutations of the C1-inhibitor gene have been described. In 85% of cases, the deficiency is due to lack

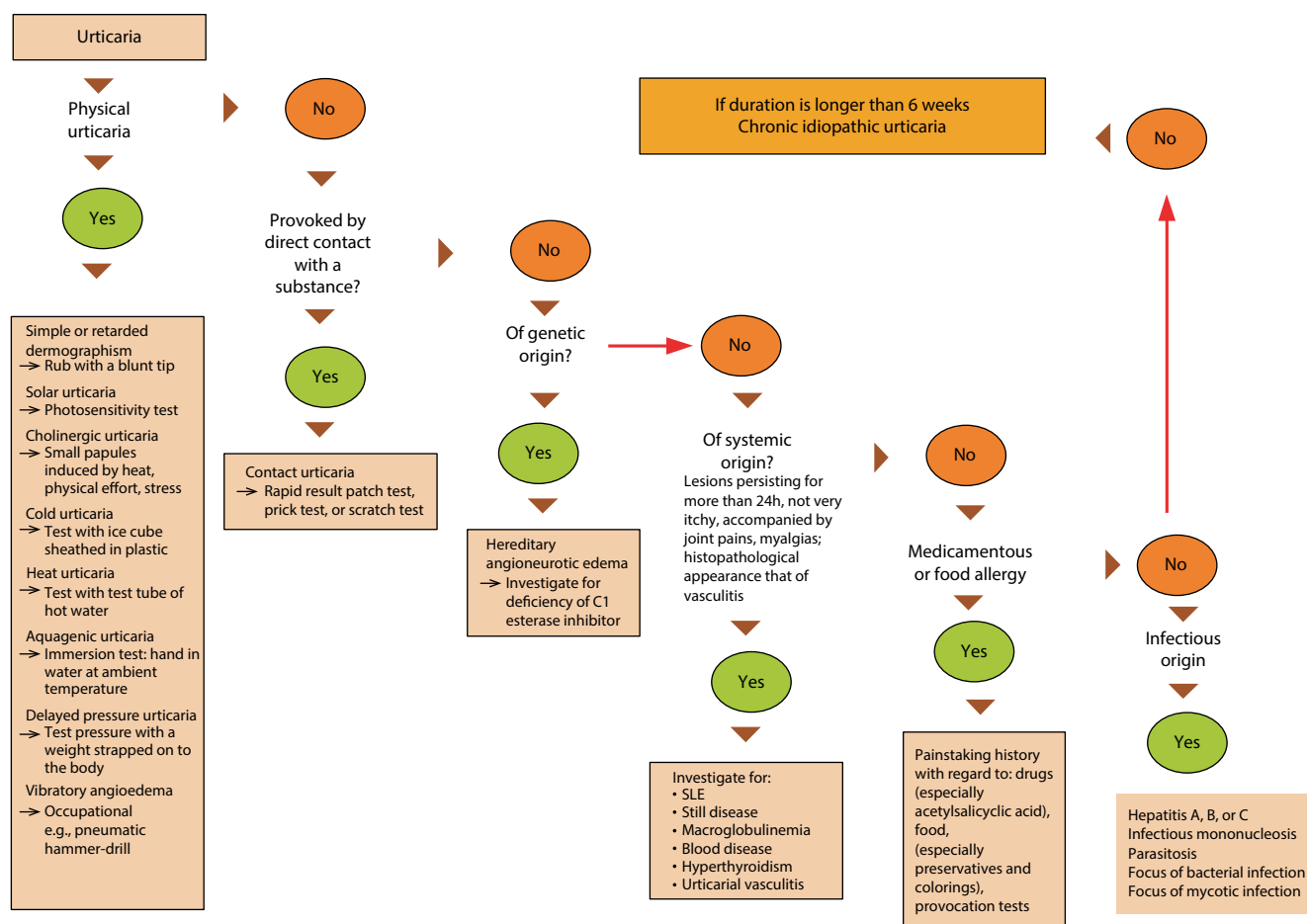


Figure 18.1 Algorithmic approach to urticaria (SLE, systemic lupus erythematosus). (Adapted from Lachapelle, J.M., Tennstedt, D., Marot, L., *Atlas of Environmental Dermatology*, UCB Pharma, Braine-l'Alleud, Belgium, 1997.)

Table 18.1 Physical Urticarias

Pressure	e.g., dermatographism
Cold	
Heat	
Solar	
Cholinergic	
Aquagenic	

of C1 esterase inhibitor; in the remainder, a malfunction to C1 inhibitor is the cause. A spontaneous mutation is found in up to 25% of cases.⁷

Worldwide, the incidence of hereditary angioedema varies between 1:10,000 and 1:150,000. Seventy-five percent of patients present before the age of 15 years.

In contrast to urticaria, angioedema affects both the reticular dermis and subcutaneous tissues. Recent data suggest that histamine-releasing immunoglobulin G (IgG) antibody directed against ϵ region of the constant fragment (F_c), or anti-F_c ϵ antibodies are the cause of the disease, removal or suppression by immunomodulation being followed by remission.⁸

Most patients with hereditary angioedema have a personal or family history of recurrent attacks of angioedema

Table 18.2 Nonphysical Urticarias

Food allergens	Fish, shellfish (lobster, shrimp, crab), eggs, dairy products, chocolate, nuts (especially peanuts), strawberries, pork, tomatoes, apples, oranges, bananas, celery, beans
Food additives	Tartrazine, food dyes, sodium benzoate, MSG
Salicylates	Aspirin, mesalazine, sulfasalazine, NSAIDs
Other drugs	Penicillins, cephalosporins, blood products, vaccines, insulin
Infection	Bacterial, viral, protozoal, helminthic
Systemic disorders	Autoimmune and collagen-vascular diseases, reticuloses, SLE
Contact urticaria	Meat, fish, vegetables, plants (common stinging nettle, poison ivy, giant hogweed, sumac), animals, insects, caterpillars
Papular urticaria	Site of insect bites, bee sting
Inhalants	House dust mite, animal dander, feathers, grass ²

Notes: MSG, monosodium glutamate; NSAIDs, nonsteroidal antiinflammatory drugs; SLE, systemic lupus erythematosus.

or abdominal pain. An important exception to this is where a spontaneous mutation has occurred. Attacks are often precipitated by trauma including surgical procedures, pregnancy, viral illness, emotional stress, and drugs such as estrogen and angiotensin-converting enzyme (ACE) inhibitors. The combination of ACE inhibitors and estrogens is contraindicated.

Cutaneous angioedema of the extremities is the first presenting sign in 75% of patients. The edema tends to be recurrent, is nonpitting in nature, and demonstrates a rapidly expanding unifocal, indurated swelling that is painful rather than pruritic. Urticaria is not part of the syndrome. The areas usually affected are the extremities, genitalia, and face. Twenty-five percent of patients also suffer from gastrointestinal (GI) symptoms including abdominal cramps, nausea, vomiting, colic, and (occasionally) signs of obstruction.

Cutaneous signs of angioedema usually develop gradually over 12–36 hours and may last up to 5 days, whereas the GI symptoms usually subside with 24 hours. Conversely, upper airway obstruction may develop rapidly within 20 minutes of onset resulting in an acute respiratory syndrome that may prove fatal. Up to 40% of all undiagnosed patients die as a result of upper airway obstruction.

MASTOCYTOSIS

Mastocytosis is a condition of unknown etiology characterized by an excessive accumulation of mast cells in various body organs and tissues. Mastocytosis occurs in three forms: (1) mastocytoma (a benign cutaneous tumor); (2) urticaria pigmentosa that is characterized by multiple colored or brown macules or papules that urticate when stroked and may become vesicular or even bullous; and (3) systemic mastocytosis in which there are mast-cell infiltrates in the skin, lymph nodes, liver, spleen, GI tract, and bones.

Patients with mastocytosis suffer from arthralgias, bone pain, and anaphylactoid reactions. Other symptoms result from overstimulation of H₂ histamine receptors, leading to peptic ulcer disease and chronic diarrhea.⁹

ANAPHYLAXIS

Anaphylaxis is an acute systemic reaction that occurs in a previously sensitized person who is reexposed to the sensitizing antigen. The most common antigens are foreign serum, parenteral enzymes, blood products, beta-lactam antibiotics, other drugs, and wasp and bee stings. Anaphylaxis may be aggravated or even induced by exercise. It is an IgE-mediated reaction that occurs when antigen (foreign protein, polysaccharide or hapten coupled with a carrier protein) reaches the circulation. Leukotrienes, histamine, and other mediators are generated or released when the antigen reacts with IgE on sensitized mast cells and basophils. These mediators cause smooth muscle contraction responsible for wheeze and GI symptoms as well as vascular dilatation that leads to circulatory collapse. Capillary leakage into the tissues causes urticaria and angioedema and results in a further decrease in the plasma volume leading to shock. Fluid may leak into the alveoli and produce pulmonary edema. Obstructive angioedema of the upper airway may also occur. Finally, profound hypotension may result in arrhythmia and cardiogenic shock.

Typically, the patient feels uneasy for approximately 1–15 minutes after exposure to the allergen. The patient then

becomes more agitated and flushed. He or she may experience palpitations, paresthesias, pruritus, throbbing in the ears, coughing, sneezing, and difficulty in breathing due to laryngeal edema or bronchospasm. Urticaria and angioedema may be evident. Nausea, vomiting, and abdominal pain and diarrhea are less common. Shock develops within another 1–2 minutes, and the patient may become incontinent, convulse, and lose consciousness.

CLINICAL AND LABORATORY AIDS REQUIRED FOR DIAGNOSIS

Urticaria

Urticaria is a clinical diagnosis. In urticaria, pruritus (generally the first symptom) is followed shortly by the appearance of wheals that may remain small (1–5 mm) or may enlarge. The larger ones tend to clear in the center and may be noticed first as large rings (>20 cm across) of erythema and edema. Ordinarily, crops of hives come and go; a lesion may appear in one site for several hours, then disappear only to reemerge at another site later. The changing morphology of lesions that may evolve over minutes to hours may lead to geographic or bizarre patterns.

The cause of acute urticaria is usually self-evident. Even when it is not so obvious, a diagnostic investigation is seldom required due to the self-limiting nature of the eruption.

In cases of chronic urticaria, a careful history, examination, and screening tests should be carried out to eliminate possible underlying systemic lupus erythematosus, polycythemia rubra vera, vasculitis syndrome, or infection. A few patients with intractable urticaria are hyperthyroid. A serum-sickness-like prodrome with urticaria may be associated with acute hepatitis B. Quantitative immunoglobulins, cryoglobulins, cryofibrinogens, and antinuclear antibodies are often sought in cold urticaria but rarely found. Although often suspected, controllable psychogenic factors are rarely identified.

The histologic changes may be very slight but usually there is edema, vascular and lymphatic dilatation, and a variable perivascular cellular infiltrate of lymphocytes, monocytes, polymorphs, and histiocytes. On electron microscopy, dermal mast cells show signs of degranulation. Various vasoactive substances are thought to be involved including histamine, kinins, leukotrienes, prostaglandins, and complement.

Urticarial lesions lasting more than 24 hours raise the possibility of this being a vasculitic disorder. Urticarial lesions of vasculitic etiology are more fixed than in classical urticaria. They last for 2–3 days and are frequently accompanied by joint pains and fever. Reduced serum complement levels with raised inflammatory markers are observed. A skin biopsy is most useful in these circumstances as urticarial vasculitis is an uncommon entity.

ANGIOEDEMA

Angioedema represents a more diffuse swelling affecting the loose subcutaneous and/or submucosal tissues. The dorsum of the hands or feet, eyelids, lips, and genitalia are the usual sites affected. Involvement of the mucous membranes may present as wheeze or stridor that may be mistaken for asthma. Edema of the upper airway is potentially life threatening.

The diagnosis of hereditary angioedema is made by measuring complement C4 levels, which remain low, even between attacks. This test carries 100% sensitivity and 100% negative

predictive value in an untreated patient and is therefore a most useful screening test. A low C1 inhibitor level will confirm the diagnosis. If the C1 inhibitor is unexpectedly normal, a C1 functional assay can be performed.

MASTOCYTOSIS

In localized mastocytosis, the histamine content in tissue is usually high, commensurate with the elevated mast cell concentration. In systemic mastocytosis, urinary excretion of histamine and its metabolites are high. Plasma histamine and prostaglandin D₂ may also be elevated.

ANAPHYLAXIS

The diagnosis of anaphylaxis is usually self-evident when there has been exposure to a known allergen. In the case of unknown exposure, increased IgE and serum tryptase levels will strongly support the diagnosis. It is worth remembering, however, that anaphylaxis may be immediate or delayed. Even in the case of a bee sting, anaphylaxis may be delayed for up to 20 minutes due to the rate of absorption of the toxin from the embedded sting sac. Acute life-threatening edema of the airway can occur more immediately, when there is local swelling following a bee or wasp sting to the pharynx, which may occur when the insect has inadvertently fallen into a beer can or glass and is unknowingly drunk by the unsuspecting partygoer.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for urticaria and angioedema includes persistent papular eruptions from insect bites such as flea or gnat bites. These eruptions can usually be distinguished from the urticarias by their central punctum.

Contact urticaria may be caused by a host of substances varying from chemicals to foods to medications, but it is usually limited to areas exposed to the contactant. Streaked urticarial lesions may be seen in acute allergic plant dermatitis (e.g., poison ivy, oak, or sumac). Phytophotodermatitis is caused by the exposure of skin to plant extracts and sun and is common in hot climates (e.g., where lime juice is used in cocktails). The possibility of porphyria should be considered in any sun-related pruritic reaction.

Contact with caterpillars can result in lepidopterism due to caterpillar toxin released from the tufts of the hairy coat (Figure 18.2). Deaths have been reported from *Lonomia* spp. that are endemic in parts of Brazil.

The differential diagnosis for anaphylaxis includes all causes of shock (e.g., acute internal hemorrhage, sepsis syndrome, cardiogenic shock) and the Waterhouse-Friderichsen syndrome following adrenal hemorrhage.

THERAPY

Urticaria

Acute urticaria is a self-limited condition that generally subsides in 1–7 days. Treatment is chiefly palliative. If the etiological trigger is known, it should be avoided. A specific exclusion diet (e.g., salicylate and tartrazine free) may be helpful. If the cause is not apparent, all nonessential drugs should be discontinued until the reaction has subsided.^{10,11}

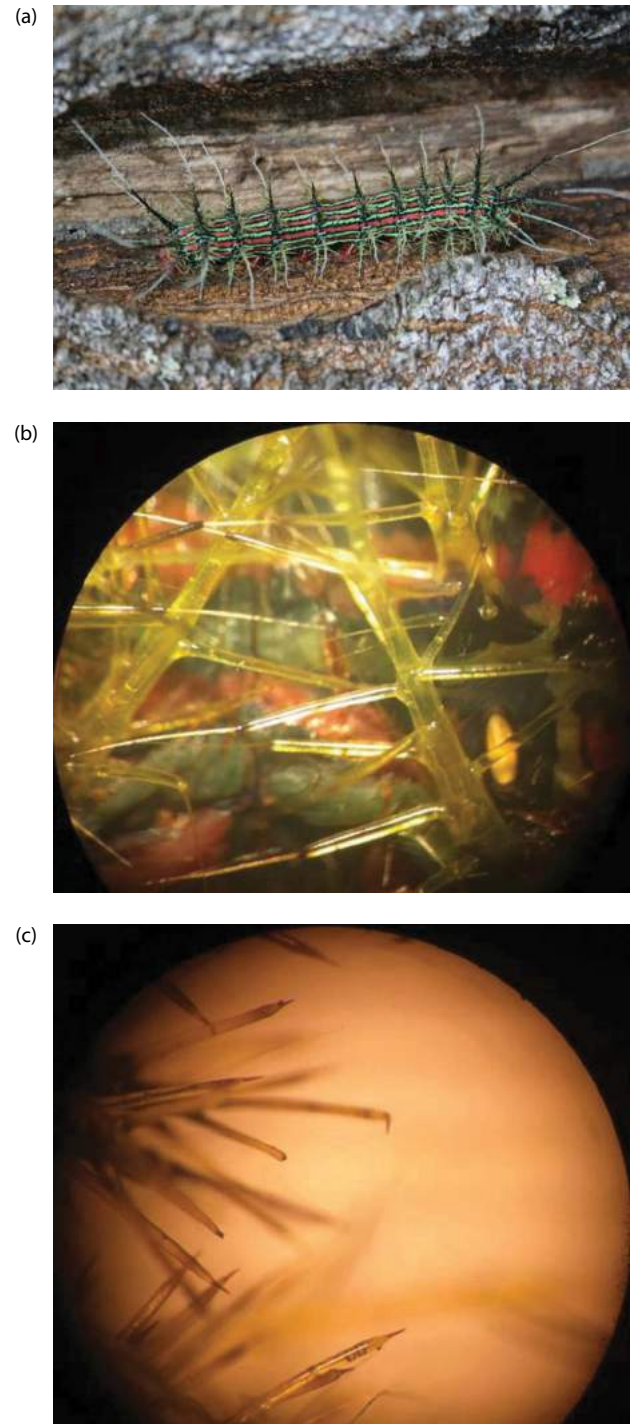


Figure 18.2 (a) Lepidopterism is a form of severe urticaria following contact with certain species of caterpillar and is due to release of toxin from hair tufts. (b) and (c) Micrograph of hairs tufts from toxic caterpillar. (Courtesy of A Kumar.)

If treatment is indicated, the initial management will include H₁ antihistamines. Doses should be increased weekly to tolerance. Antihistamines from different classes may be systematically tried if initial choice is ineffective or intolerable. A combination of two or more antihistamines acting at

different receptor sites may offer additional benefit over and above a single agent.

Most symptoms can usually be relieved with diphenhydramine 50–100 mg every 4 hours, hydroxyzine 25–100 twice a day, or cyproheptadine 4–8 mg every 4 hours. Hydroxyzine is the preferred drug for cholinergic urticaria.

Terfenadine (60 mg b.i.d.) is a nonsedating antihistamine that has been reported to be effective in chronic idiopathic urticaria. It is metabolized by multiple cytochrome P-450 enzymes, thus limiting the potential for serious drug-drug interactions¹²; however, concomitant use with erythromycin (and related macrolide antibiotics) or ketoconazole (and related imidazole) leads to increases in the plasma levels that may cause cardiac arrhythmias. Terfenadine is not recommended in lactating or pregnant women.

Another nonsedating antihistamine, astemizole, has been reported to be effective in the majority of patients with seasonal allergic rhinitis and chronic idiopathic urticaria.¹³ The long half-life of astemizole is a major disadvantage if skin-prick testing is needed or if the patient becomes pregnant while on therapy. A less sedating antihistamine approved for use is loratadine in a dosage of 10 mg daily. It has a shorter half-life than astemizole and is similar to the other antihistamines in its effectiveness. It appears not to interact with imidazole antifungals or macrolide antibiotics.

Oral antihistamines with tranquilizing properties are usually beneficial (e.g., hydroxyzine 25–50 mg b.i.d. or cyproheptadine 4–8 mg q4–8h for adults; for children, hydroxyzine 2 mg/kg/day divided q6h, and cyproheptadine 0.25–0.5 mg/kg/day divided q6–8h).

Doxepin (a tricyclic antidepressant) 25–50 mg twice daily, or more commonly 25–75 mg at bedtime, may be the most effective agent for some adult patients. It should be used with caution because of its anticholinergic side effects and promotion of cardiac arrhythmias.

Prednisone in a dose of 40 mg daily may be necessary in more severe cases of urticaria and in cases of angioedema.¹⁰ It will usually suppress both acute and chronic forms of urticaria; however, the use of systemic glucocorticoids is rarely indicated because properly selected combinations of agents with less toxicity are usually effective. After steroids are withdrawn, the urticaria virtually always returns if it had been chronic.

Other agents with some promise as adjuvant therapy include calcium channel blockers (used for at least 4 weeks), terbutaline 1.25–2.5 mg three times a day, and colchicine 0.6 mg twice a day.

Local treatment is rarely of benefit. Starch baths twice daily or Aveeno baths, prepared by adding one cupful of finely refined cornstarch or a packet of Aveeno to a comfortably warm bath, may alleviate symptoms in some patients. Alternatively, one may use a lotion containing 0.5% camphor, 0.5% menthol, and 0.5% phenol topically or in addition to the bathing. Topical glucocorticoids are not recommended, not the least, because the application of touch and massage are likely to exacerbate symptoms.

Hereditary Angioedema

Hereditary angioedema may present as a medical emergency that requires rapid therapeutic intervention. The edema progresses until the complement components have been consumed. Iatrogenic cases are not uncommon.¹⁴

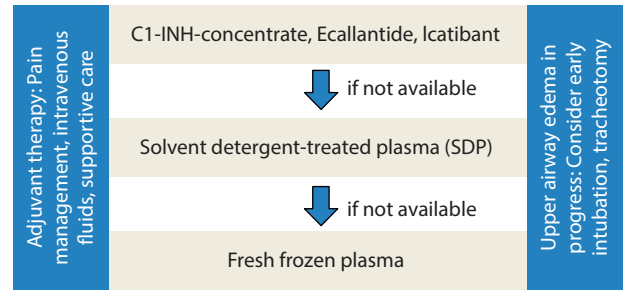


Figure 18.3 Treatment algorithm for hereditary angioedema in adults. (From WAO Guideline for the Management of Hereditary Angioedema, reference 19, under Open Access.)

Acute attacks that threaten to produce airway obstruction should be treated promptly by establishing an airway. A comprehensive consensus guideline for the management of hereditary angioedema has been published by the World Allergy Organization and recommends first-line treatment with a C1 inhibitor concentrate, such as ecallantide or icatibant¹⁴ (Figure 18.3). Treatment should be available on demand for any patient who experiences attacks affecting the upper airway and should be considered in all attacks that result in debilitation/dysfunction and/or involve the face, the neck, or the abdomen. All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer.

Treatment with plasma-derived C1 inhibitor concentrate is effective in pediatric patients and is the only approved on-demand drug for hereditary angioedema treatment in childhood (in European Union only, 12 years and older in the United States). Recombinant C1-INH, ecallantide, and icatibant are not licensed for use in children.

A partially purified C1 inhibitor fraction of pooled plasma has been shown to be safe and effective for prophylaxis (e.g., prior to a dental procedure or endoscopy). Solvent detergent-treated plasma (SDP) is preferred over fresh frozen plasma (FFP) as complement substrate in the plasma could provoke an attack although this has not been observed in symptom-free patients.

Long-term management will have to take into account both the frequency and severity of attacks as well as special circumstances, such as pregnancy, surgical procedures, and children. For long-term prophylaxis of hereditary angioedema, one of the impeded androgens should be used. Treatment is commenced with stanozolol 2 mg times a day or danazol 200 mg three times a day. When control is achieved, the dosage should be reduced as much as possible to minimize masculinizing side effects in women and reduce the cost. These drugs are not only effective but also have been shown to raise the low C1 inhibitor and C4 toward normal.

Mastocytosis

Cutaneous mastocytosis usually develops in childhood (Figure 18.4). The solitary mastocytoma will usually involute spontaneously. Urticaria pigmentosa either clears completely or is substantially improved by adolescence. These conditions rarely, if ever, progress to systemic mastocytosis. Treatment with an H₁ antihistamine is usually all that is needed.

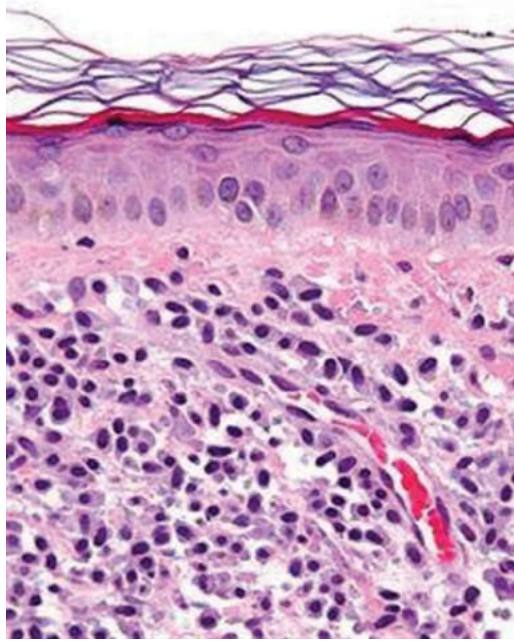


Figure 18.4 Micrograph of mastocytosis on skin biopsy (H&E stain).

If systemic mastocytosis ensues, the symptoms should be treated with an H_1 or H_2 antihistamine. Aspirin therapy may be tried, but with caution as this may enhance production of leukotrienes. For GI symptom control, oral cromolyn sodium 200 mg four times a day (100 mg four times a day for children 2–12 years old) should be given. There is no effective treatment available to reduce the number of tissue mast cells.

Anaphylaxis

Severe reactions with generalized swelling, urticaria, angioedema, dizziness, sweating, pounding headache, stomach cramps, chest tightness, and a sensation of choking or impending doom may signify impending anaphylaxis.

In cases of acute pharyngeal or laryngeal angioedema, epinephrine 1:1000, 0.5 mL by subcutaneous injection should be given immediately. Nebulized epinephrine 1:100 dilution and intravenous antihistamine (e.g., diphenhydramine 50–100 mg) will usually prevent airway obstruction. Urgent intubation or emergency tracheostomy may be required, followed by 100% O_2 therapy and resuscitation. (See Chapter 19. Allergy to bee sting is an example of a type I allergic hypersensitivity [anaphylaxis] reaction.) Confirmation that an allergic reaction has taken place can be made by measuring the serum tryptase. Most deaths will occur because of delays in accessing emergency treatment.

COURSE AND PROGNOSIS

Most episodes of acute urticaria and angioedema are acute and self-limited, resolving spontaneously over a period of 1–2 weeks. In about half the cases of chronic urticaria, spontaneous remissions occur within 2 years. Control of stress often helps to reduce the frequency and severity of episodes. Alcohol, coffee, and tobacco should be avoided, as these may aggravate the symptoms. Certain drugs, such as aspirin, may also exacerbate symptoms. When urticaria is produced by aspirin, sensitivity to other nonsteroidal antiinflammatory drugs and to foods or drugs containing the additive tartazine should be investigated.

Patients with chronic mastocytosis generally have a good prognosis. The course of an anaphylactic reaction is unpredictable and is largely determined by the speed with which the patient can access appropriate emergency services.

All patients with a history of anaphylaxis should carry a preloaded epinephrine syringe (EpiPen; 300 μ g) for emergencies. Any person with a history of allergy should wear a MedicAlert bracelet at all times bearing the details of this allergy.

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Severe, acute allergic and immunologic reactions II: Other hypersensitivities and immune defects, including HIV

Samuel H. Allen

HYPERSENSITIVITY REACTIONS

A hypersensitivity reaction (HSR) is an immune-mediated response to a drug or other substance that can result in harm. It is estimated that HSRs account for approximately 5%–10% of all drug-related adverse events. A HSR may occur only once or may recur throughout life following sensitization to a particular antigen. Four basic types of classical immune-mediated hypersensitivity have been described (Table 19.1).

Type I: Immediate (Atopic or Anaphylactic)

Type I hypersensitivity is an allergic reaction provoked by exposure to a specific type of antigen known as an allergen. Exposure may be by ingestion, inhalation, injection, or direct contact. Type I reactions are characterized by an exaggerated release of immunoglobulin E (IgE), which binds to mast cells and basophils. Later exposure to the same allergen results in cross-linking of bound IgE on the sensitized cells. This cross-linking causes degranulation and secretion of pharmacologic mediators (such as histamine, leukotriene, and prostaglandin) that act on the surrounding tissues, causing vasodilatation and smooth muscle contraction. The reaction may be local or systemic, and symptoms may vary from mild irritation to anaphylactic shock, which is the result of an acute life-threatening systemic reaction.

Examples of common type I reactions and their triggers include allergic asthma (house dust mite), hay fever (grass pollen), allergic rhinitis (animal dander), and nut and drug allergies. Because it takes some time to produce IgE antibodies, type I HSRs usually begin at least several days after starting a new drug. If a person stops the drug and restarts it later, the reaction can be immediate, because the immune system is already primed to respond to it. Conversely, HSRs can occur for the first time months or years after starting a new drug despite continuous exposure to the drug. See also Box 19.1.

Skin eruptions occur in approximately 90% of type I HSRs. The most common manifestation is a maculopapular eruption that typically develops 1–4 weeks after starting a new drug. A rash often appears first on the trunk and then spreads outward. The mucous membranes may be involved.

In Stevens–Johnson syndrome (SJS) and erythema multiforme major, patients develop blisters on the skin and mucous membranes. Other manifestations may include fever, aphthous ulcers, and infection of the eyes.

A toxic epidermal necrolysis results in extensive skin loss. Subsequent desquamation leaves raw areas that behave physiologically as burn injury. Superantigens such as toxic shock syndrome toxin 1 (TSST-1) or exfoliatin A and B that are released by *Staphylococcus aureus* bacteria trigger the release of

proinflammatory cytokines leading to necrolysis of the epidermis layer.

Fever is not an uncommon feature of drug-induced hypersensitivity. Other manifestations include soft-tissue swelling, enlarged lymph nodes, sore throat, cough, difficulty breathing, gastrointestinal (GI) symptoms, dizziness, muscle and joint pain, blood cell abnormalities, blood vessel inflammation, and liver or kidney dysfunction.

The most severe type of drug-induced allergic reaction is anaphylaxis, which can occur within seconds or minutes after restarting a drug to which the person has previously been exposed. Symptoms include hives, swelling, constriction of the upper airway, falling blood pressure, rapid heartbeat, shock, and cardiovascular collapse.

Recognition of the condition can be life-saving and both the patient and their carer(s) should be made aware of the allergy.

Treatment of anaphylaxis depends on the severity of the reaction. Anticipatory transfer for observation on a Medical High Dependency Unit (MHDU) should be considered. Intramuscular epinephrine 0.1–0.5 mg (0.1–0.5 mL of 1:1000 solution) to maintain blood pressure should be administered if the patient has signs of shock (tachycardia, hypotension, thread pulse). This should be repeated every 10–20 minutes (see Box 19.2). Antihistamines and corticosteroids are usually indicated. The provocative agent should be avoided.

If undergoing elective desensitization, this should only be undertaken in a facility that has full resuscitation equipment and by persons familiar with their use.

Type II: Antibody Dependent

In type II hypersensitivity, the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces. The antigens recognized in this way may be either intrinsic (self) or extrinsic (foreign) antigens. These cells are recognized by macrophages and dendritic cells that act as antigen-presenting cells, causing B cells to respond by producing antibodies against the foreign protein. Examples of this type of reaction include autoimmune hemolytic anemia, transfusion reactions, transplant rejection, Goodpasture syndrome, pemphigus, Graves disease, myasthenia gravis, and rheumatic fever. Because the reaction is antibody mediated, the reaction will evolve over a period of 1–3 days.

Type III: Immune Complex

Type II hypersensitivity occurs when antigens and antibodies are present in roughly equal measure, causing extensive

Table 19.1 Types of Hypersensitivity Reaction

Type	Alternative name	Associated disorders	Mediator(s)
I	Allergic	Atopy, anaphylaxis, asthma	IgE
II	Cytotoxic, antibody dependent	Erythroblastosis fetalis, Goodpasture syndrome, autoimmune hemolytic anemia	IgM or IgG (complement)
III	Immune complex disease	Serum sickness, Arthus reaction, SLE	IgG (complement)
IV	Cell mediated	Contact dermatitis, tuberculosis, chronic transplant rejection	Cell mediated

Box 19.1 Allergy to Bee Sting as an Example of a Type I Allergic Hypersensitivity (Anaphylaxis) Reaction

Insects of the order *Hymenoptera* include wasps and bees. Stinging is a defense mechanism designed to incapacitate other insects. Bees differ from wasps in that their stinging apparatus is inserted into the victim on stinging. Sting venom comprises proteolytic enzymes, phospholipases, metalloproteinases, and toxins. Antigen 5 (or Ves g V) from yellow jacket wasps (*Vespula germanica*) and phospholipase (Api m II) from honeybees (*Apis mellifera*) are the major allergy-provoking venom components. Sensitization to insect venom can occur after a single sting. Although cross-reaction allergy can occur, most people remain allergic to either wasp or bee, but not both.

Pain, redness, and swelling normally occur at the site of a sting. This is not an allergy, but rather a local toxic reaction to the venom. This reaction evolves over a period of a few hours and settles within 1–2 days without any adverse consequences. A more immediate and severe reaction can occur, however, in an individual who has been sensitized by a previous wasp or bee sting. If allergic, he or she may develop a reaction that can vary from mild localized swelling to life-threatening anaphylaxis. Typically there is localized redness and swelling spanning two joints, intense itching, and pain.

More severe reactions cause generalized swelling, urticaria, angioedema, dizziness, sweating, pounding headache, stomach cramps, chest tightness, and a sensation of choking and/or impending doom. Symptoms may develop up to 20 minutes after the sting. This represents the time between the release of the sting and the effect of the venom components on the victim following the insect attack.

If stung by a bee, the sting sac will continue to actively pump venom if left in situ; therefore, if the stinging apparatus is visible, it should be carefully extricated from the flesh of the victim to prevent further toxin release. The sac should be removed without squeezing. The honeybee (*Apis* spp.) is unique in that it possesses a barbed stinging organ. The female honeybee, however, carries the stinger and dies shortly after discharging a sting.

TREATMENT OF WASP OR BEE STING ALLERGIC REACTION

A double dose of oral antihistamine, such as chlorpheniramine 8 mg, should be administered in adults and older children. In the case of a generalized reaction, one should

administer immediate intramuscular chlorpheniramine 10 mg, oral corticosteroid (prednisone 30 mg) and give a β -agonist inhaler or nebulizer.

In the case of shock or respiratory difficulties, 0.5 mL of intramuscular epinephrine (1:1000) plus intramuscular chlorpheniramine 10 mg and hydrocortisone 200 μ g should be administered and arrangements made to transport the patient to a suitable treatment facility.

All patients with a history of allergy should carry a pre-loaded epinephrine syringe (EpiPen 300 μ g) for emergencies. Repeat injections should be administered every 5 minutes until a satisfactory response is achieved. For children younger than 5 years, 0.1–0.3 mL of epinephrine (1:1000) should be administered according to size and age, and arrangements made to transport the child to an emergency department for further monitoring. Confirmation that an allergic reaction has taken place can be made by measuring the serum tryptase.

A person known to be wasp or bee allergic should have a MedicAlert bracelet carrying details of this allergy.

DESENSITIZATION

Venom desensitization immunotherapy is a useful means of treatment for patients with severe generalized venom allergy and is particularly useful for beekeepers, horticulturists, and gardeners. Weekly injections are given during the initial treatment phase and then monthly for another 3 years. At the end of the therapy the patient should be able to tolerate 100 μ g of venom—equivalent to two bee stings—with no adverse reaction. This therapy should be carried out only in specialist clinics where resuscitation facilities are available, because there is a small risk of inducing an allergic reaction. Anti-wasp and anti-bee venom vaccines are available, but these are wasp and bee species-specific.

Box 19.2 Pediatric Dose for Allergic Reaction

Infants to 2 years: 0.05–0.1 mL IM or subcutaneously of 1:1000 solution. If after 10 minutes from the first injection symptoms are not noticeably improved, administer a second dose.

Children:

2 to 5 years: 0.15 mL IM or subcutaneously
6 to 11 years: 0.2 mL IM or subcutaneously
12 years older: 0.3 mL IM or subcutaneously

If after 10 minutes from the first injection symptoms are not noticeably improved, administer a second dose.

cross-linking. Large immune complexes that cannot be cleared are deposited in tissue to induce an inflammatory response. The reaction develops over days to weeks. Examples of this type of reaction include rheumatoid arthritis, serum sickness, systemic lupus erythematosus (SLE), Arthus reaction, farmer's lung, and polyarteritis nodosa.

Type IV: Cell Mediated (Delayed-Type Hypersensitivity)

Type IV hypersensitivity is often called delayed type as the reaction takes 2–3 days to develop. Unlike other types, it is not

antibody mediated but rather represents a type of cell-mediated response.

Cytotoxic (CD8+) and helper (CD4+) T cells recognize antigens in a complex with the major histocompatibility complex molecules class I or II, respectively. The antigen-presenting cells are macrophages or dendritic cells that secrete interleukin-12 (IL-12). This secretion stimulates further CD4+ T-cell proliferation. These T cells secrete IL-2 and interferon- γ , inducing type I cytokines. Activated CD8+ cells destroy target cells, and activated macrophages transform into multinucleated giant cells. This type of reaction is seen in contact dermatitis (e.g., poison ivy), atopic dermatitis, leprosy, and tuberculosis. The Mantoux test for testing prior exposure to tuberculosis antigen is an example of a delayed-type HSR.

IMMUNE DEFECTS

Deficiencies of the immune system may result in recurrent infections, autoimmunity, and susceptibility to malignancy. Although intrinsic congenital immunodeficiencies are rare, the widespread use of corticosteroid and immunosuppressive therapies as well as the spread of the human immunodeficiency virus (HIV) pandemic means that the dermatologist is increasingly being called to assess problems relating to immunosuppression. In the context of an immune defect, the patient is often systemically unwell.

Immunodeficiency may be congenital or acquired (Table 19.2). Dysfunction may occur in either the quantitative (number of cells) or the qualitative (function of cells) aspect. These aspects include deficiencies of

- Neutrophils (and monocytes/macrophages)
- Complement pathway
- B-cell defects (causing antibody deficiency)
- T-cell defects (causing impaired cell-mediated immunity)
- Combinations of any of the preceding aspects

More than 100 different primary congenital immunodeficiencies due to specific genetic defects have been described¹; most are rare. They usually present in childhood, but some types and the less severe forms may not become apparent until adulthood. Much more common are acquired immunodeficiencies, which can result from malnutrition, splenectomy, immunosuppressive therapy, drug side effects, and/or infection. The most common infective cause is HIV, which leads to acquired immune deficiency syndrome (AIDS).

Opportunistic infections occur when there is weakness of host defense mechanisms regardless of the cause. The nature of the infection may sometimes indicate the specific type of immune defect (Table 19.3). Opportunistic infections usually present insidiously. An underlying immune defect should be suspected in patients presenting with recurrent infections, particularly with unusual organisms or at unusual sites (Table 19.4).

Defects in Neutrophils

Defects of neutrophils result in a predisposition to bacterial infections that results in extracellular infection. The risk of infection rises steeply once the neutrophil count falls below $0.5 \times 10^9/L$. The gut is normally colonized with potentially pathogenic bacteria that can readily lead to septicemia following immunosuppression from whatever cause. The duration of neutropenia can be reduced by use of granulocyte

Table 19.2 Congenital and Acquired Immunodeficiencies

Congenital	Acquired
Neutrophil deficiency	
Congenital neutropenia	Drug-induced myelosuppression
Cyclical neutropenia	Hypersplenism
Leukocyte adhesion defects	Autoimmune neutropenia
Hyper IgE syndrome	Corticosteroid therapy
Shwachman syndrome	Diabetes mellitus
Chronic granulomatous disease	Hypophosphatemia
Storage diseases	Myeloid leukaemia
Chediak-Higashi syndrome	Influenza
Complement deficiency	
C3, C1q, I, H deficiency	
C5, 6, 7, 8, 9 deficiencies	
Mannan-binding lectin deficiency	
Antibody deficiency (B-cell defects)	
X-linked hypogammaglobulinemia	Myeloma
Common variable immunodeficiency	Lymphoma
Specific IgA deficiency	Splenectomy
Specific antibody deficiency	Congenital rubella
T-cell deficiencies	
DiGeorge anomaly	Measles
IL-2 deficiency	Corticosteroids
Signal transduction defect	Calcineurin inhibitors (e.g., cyclosporine)
Combined T- and B-cell deficiencies	
Severe combined immunodeficiency	Protein-calorie malnutrition
Wiskott–Aldrich syndrome	Immunodeficiency of prematurity
Ataxia telangiectasia	HIV/AIDS
Hyper IgM syndrome	
Duncan syndrome	

Table 19.3 Immune Defects and Associated Opportunistic Infections

Neutrophil deficiency	
<i>Staphylococcus aureus</i>	Coagulase-negative staphylococcus
<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>
<i>Pseudomonas aeruginosa</i>	<i>Serratia marcescens</i>
<i>Bacteroides</i> spp.	<i>Aspergillus fumigatus</i>
<i>Candida</i> spp. (systemic)	<i>Mucor</i> spp.
<i>Absidia</i> spp.	
B-cell (antibody) deficiency	
<i>Campylobacter</i> spp.	Echovirus
<i>Mycoplasma</i> spp.	<i>Ureaplasma</i> spp.
Complement deficiency (lytic pathway C5–C9)	
Meningococcus	Gonococcus (disseminated)
T cell-mediated immunodeficiency	
<i>Listeria monocytogenes</i>	<i>Legionella pneumophila</i>
<i>Salmonella</i> spp. (nontyphi)	<i>Nocardia</i> spp.
<i>Mycobacterium tuberculosis</i>	Atypical mycobacteria spp.
<i>Candida</i> spp. (mucocutaneous)	<i>Toxoplasma gondii</i>
<i>Cryptococcus neoformans</i>	<i>Histoplasma capsulatum</i>
<i>Pneumocystis jiroveci</i>	Herpes simplex
Herpes zoster	Measles virus
Cytomegalovirus	Epstein–Barr virus

Table 19.4 Warning Signs of Immune Deficiency

- Eight respiratory tract infections/year in a child
- >4 respiratory tract infections/year in an adult
- >1 infection requiring hospital admission or intravenous antibiotics
- Infections with unusual organisms
- Infections at unusual sites
- Chronic infection unresponsive to usual treatment
- Early end-organ damage (e.g., bronchiectasis)
- Positive family history

colony-stimulating factor or granulocyte-macrophage colony-stimulating factor. Prompt antiinfective therapy for febrile episodes during neutropenia is essential. Preemptive prophylaxis prescribed to commence postchemotherapy was advocated in the past before the specter of antimicrobial drug resistance, which is an emerging worldwide problem.² A particular and typically benign variant of neutropenia is cyclical neutropenia, which produces cycles of neutropenia every 3–5 weeks.

Defects of neutrophil function include autosomal recessive congenital leukocyte adhesion defect, hyper-IgE syndrome, and Shwachman syndrome that may resemble cystic fibrosis. Hyper-IgE syndrome produces recurrent frequent staphylococcal boils and furuncles—hence, its synonym, Job syndrome—and is associated with elevated levels of IgE. Unusual eczema-like skin eruptions and severe lung infections resulting in pneumatoceles may occur. Many patients with autosomal dominant hyper-IgE syndrome fail to lose their baby teeth and have two sets simultaneously.

Chronic granulomatous disease usually presents in early or late childhood. Patients present with chronic suppurative granulomas or abscesses affecting the skin, lymph nodes, and sometimes the lung and liver, as well as osteomyelitis. Because macrophages are also affected, cell-mediated opportunistic infections may also be seen, such as atypical mycobacteria, *Nocardia*, and salmonellae. Diagnosis is established by the nitroblue tetrazolium test.

Complement Deficiency

Complement deficiencies are rare. They can be associated with increased susceptibility to infection with *Haemophilus* and pneumococcal infection, especially in early childhood prior to development of a sufficiently wide specific antibody repertoire.

There are two major patterns of infection associated with complement deficiency: Deficiencies of C3, C1q, or factors I or H give rise to an increased susceptibility to capsulated bacteria, such as *Haemophilus influenza*, pneumococcus, meningococcus, and Group B streptococcus. These patients may also develop SLE-like immune complex disorders. Conversely, deficiency of the lytic complement pathway, C5–9, causes susceptibility to disseminated neisserial infections, meningococemia, and gonococemia. C1 esterase inhibitor deficiency is not associated with infection but with hereditary angioedema (see Chapter 18).

B-Cell Defects (Antibody Deficiency)

In X-linked hypogammaglobulinemia, B cells and plasma cells are reduced resulting in a profound reduction in all the immunoglobulin classes. T cells are normal. The specific gene defect

is found on the X chromosome. X-linked hypogammaglobulinemia typically presents with infections such as meningitis and mycoplasma infection after the first 3–6 months of life, when passively transferred maternal antibody has largely been lost. Intravenous immunoglobulin (IVIg) replacement therapy is successful, and most patients are able to treat themselves at home.

Common variable immunodeficiency is a late-onset antibody deficiency that may present in childhood or adult life. Immunoglobulin G (IgG) levels are especially low. It is similar to X-linked hypogammaglobulinemia, but a particular feature is lymph-node hyperplasia that may express itself as nodular lymphadenopathy and lymphoreticular malignancy. The findings of reduced immunoglobulin levels with normal B-cell numbers indicate the diagnosis. Regular immunoglobulin replacement therapy (IVIg) with antimicrobials for opportunistic infection is the mainstay of management.

Specific immunoglobulin A (IgA) deficiency is common, affecting approximately 0.4% of the general population. Most cases are asymptomatic, but some patients have an associated celiac disease or other autoimmune disorder.

Hypogammaglobulinemia is seen in the immune paresis of patients with myeloma and chronic leukemia or lymphoma. Splenectomy causes impaired defense against encapsulated bacteria, most notably *Streptococcus pneumoniae* but also *Haemophilus* and *Neisseria* spp., with risk of fulminant sepsis *Capnocytophaga canimorsus*, which is almost exclusively observed after close contact with dogs (bites, scratches, or even saliva exposure) and severe babesiosis, a tick-borne illness that is endemic in parts of the U.S. Northeast, is also more common in asplenic persons. Hyposplenism associated with severe sickle cell disease is responsible for the increased risk of infection in such patients. Pneumococcal, meningococcal, and *Haemophilus influenzae* type B (Hib) vaccination before elective splenectomy and the use of penicillin prophylaxis (penicillin V 250 mg once daily) can largely eliminate the risk of serious infection. Hypogammaglobulinemia can also occur in congenital rubella.

T-Cell Defects

DiGeorge syndrome (22q11 deletion syndrome) occurs in 1 in 4000 live births. It is a defect of branchial arch development leading to abnormal thymic growth. Associated features include dysmorphic facies, hypoparathyroidism, and cardiac defects. Patients present with features of impaired T cells including mucocutaneous candidosis and *Pneumocystis jirovecii* pneumonia (PcP), often with chronic diarrhea due to a variety of pathogens. The absent thymus can be documented radiologically. CD3+ and CD4+ T-cell subsets are reduced, and T cell-proliferative responses are impaired. Immunoglobulin production is usually normal. Management entails prompt treatment of opportunistic infections. Thymic transplant and bone-marrow transplant have had some success.

Combined B- and T-Cell Defects

The most severe immunodeficiencies are those that affect both B- and T-cell responses. These immunodeficiencies can stem from a variety of defective mechanisms but tend to have rather similar clinical features, combining the opportunistic

infections of cell-mediated immunodeficiency with those of antibody deficiency.

Severe combined immunodeficiency (SCID) syndrome usually presents in the first weeks of life. Failure to thrive, absent lymphoid tissue, lymphopenia, and hypogammaglobulinemia with multiple severe infections are typical. Immunoglobulin therapy is effective for the antibody deficiency, but the cell-mediated opportunistic infections are the main determinants of outcome. Bone-marrow transplantation is the definitive approach and has had significant success, especially if carried out early in the disease course. More recently, gene therapy and attempts to correct adenosine deaminase deficiency associated with SCID have had some success.

Failure of class switching from immunoglobulin M (IgM) to other classes of antibody leads to normal or high levels of IgM associated with low IgG and IgA. T-cell function is impaired, leading to opportunistic infection with *P. jirovecii*, *Cryptosporidium* (including sclerosing cholangitis), herpes virus infections, candidosis, and cryptococcosis.

Wiskott–Aldrich syndrome is an X-linked, mainly cell-mediated defect associated with falling immunoglobulins. Clinical features may include eczema, thrombocytopenia, autoimmune defects, and lymphoreticular malignancies.

Epstein–Barr virus (EBV)-associated immunodeficiency (Duncan syndrome) results in polyclonal EBV-driven lymphoproliferation, combined immunodeficiency, aplastic anemia, and lymphoid malignancy.

HIV AND AIDS

AIDS was first recognized in 1981.^{3,5} It is caused by human immunodeficiency virus-1 (HIV-1). HIV-2 causes a similar illness to HIV-1 but is less aggressive and restricted mainly to western Africa.

In 2015, the World Health Organization estimated that there were 36.7 million people living with HIV/AIDS.⁴ An estimated 39 million people have died from the disease, the vast majority of which have been in sub-Saharan Africa.

Combination therapy, composed of three active drugs (“triple cocktail”) from two or more different drug classes, constitutes highly active antiretroviral therapy (ART). As of 2016, there is a wide choice of well-tolerated and efficacious HIV therapies offering the patient the potential for lifelong suppression of viral replication, even if the prospect of achieving eradication of the virus, either through a vaccine or potent combination therapy, remains elusive. A number of these are offered as coformulated once daily single tablet regimens (Table 19.5).

Natural History of HIV and AIDS

Without treatment, a person with HIV may develop one or more opportunistic infections and/or cancers.⁶ Death results from these illnesses, which the HIV has made the body more vulnerable to, and not directly from the HIV virus itself (Figure 19.1).

HIV Seroconversion

HIV seroconversion illness develops in approximately 75% of persons following acute infection with HIV. It occurs 2–6 weeks after exposure and lasts a few days to several months but usually less than a fortnight. The symptoms are nonspecific but

Table 19.5 Antiretroviral Drug Classes

Drug class	Drug	(abbreviation)
Single tablet regimens (STR)	Atripla®	EFZ/FTC/TDF
	Complera®	RPV/FTC/TDF
	Stribald®	EVG/COBI/FTC/TDF
	Triumeq®	DTG/ABC/3TC
	Genvoya®	EVG/COBI/FTC/TAF
	Odefsey®	RPV/FTC/TAF
Nucleotide/nucleotide reverse transcriptase inhibitors “nukes” (NRTI/NtRTI)		
	Abacavir	ABC
	Emtricitabine	FTC
	Lamivudine	3TC
	Zidovudine	AZT
	Tenofovir disoproxil	TDF
NRTI fixed dose combinations	Epzicom®	ABC/3TC
	Trizivir®	ABC/3TC/AZT
	Truvada®	FTC/3TC
	Descovy®	FTC/TAF
	Combivir®	3TC/AZT
Integrase inhibitors (INSTI)	Raltegravir	RAL
	Dolutegravir	DOL
Non-nucleoside reverse transcriptase inhibitors “non-nukes” (NNRTI)		
	Efavirenz	EFZ
	Rilpivirine	RPV
	Etravirine	ETR
	Nevirapine	NVP
Protease inhibitors (PI)	Darunavir	DRV
	Atazanavir	ATZ
	Fosamprenavir	FOS
	Kaletra®	LPV/RTV
	Prezcobix®	DRV/COBI
	Evotaz®	ATZ/COBI
CCR5 inhibitor	Maraviroc	MVC
Booster drugs	Cobicistat	COBI
	Ritonavir	RTV

may mimic a flu-like illness with headache. It can be mistaken for infectious mononucleosis with lassitude, fever, arthralgia, myalgia, and lymphadenopathy. Weight loss, nausea, and diarrhea are common. Rarely, presentation may be neurological (aseptic meningitis, Bell palsy, encephalitis, myelitis, polyneuritis, or Guillain–Barré syndrome). Diagnosis is confirmed by a positive HIV polymerase chain.

The principal dermatologic manifestation, occurring in up to 75% of cases of acute seroconversion, is a nonspecific eruption. This usually appears as a maculopapular erythematous exanthem, notably of the face, palms, and soles (Figure 19.2). Painful oral ulceration, genital ulceration, erythema multiforme, and SJS may occur. There is often an associated hepatitis with transient derangement of liver transaminases and mild anemia. Skin biopsy shows nonspecific mild inflammatory changes.



Figure 19.1 Rash of seroconversion illness.

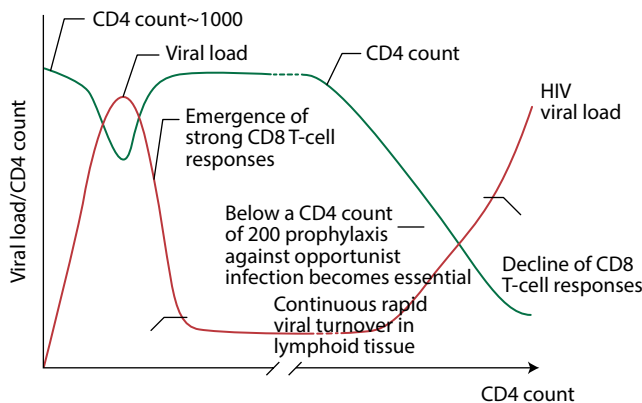


Figure 19.2 Natural history of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS).

An acute decrease in the CD4+ count at seroconversion coincides with a surge in plasma HIV RNA levels to more than 1 million copies/mL. The decrease in the CD4+ count may be sufficient to allow opportunistic infections to occur. Due to the exceedingly high HIV viral load at this time, the patient is highly infectious should he or she engage in sexual activity. It is estimated that one-quarter of HIV transmission occurs during this time; therefore, any attempts to intervene and interrupt viral replication at this early stage would have benefits not only for the individual but also as a public health intervention.

Without treatment, the median time to develop AIDS is approximately 8 years. This asymptomatic phase is called the "latent period." Many patients will be unaware of their HIV

status during this time and may unwittingly pass on their infection. Now that treatments are well tolerated and the long-term benefits of treatment outweigh the potential risk of delaying therapy, treatment as prevention (TasP) will become the standard of care for all persons living with HIV irrespective of their CD4+ count.⁷

SPECIFIC SKIN CONDITIONS IN HIV INFECTION

Virtually all dermatologic conditions are more common and more severe in HIV infection. Unusually florid skin infections, neoplasias, drug reactions, and other unusual eruptions form the bulk of dermatologic manifestations (Table 19.6). Early HIV-associated diseases include xerosis with pruritus, seborrheic dermatitis, and an itchy folliculitic dermatitis that may be fungal (*Malassezia furfur*), staphylococcal, or eosinophilic in etiology.

Many of the skin manifestations of HIV are HIV indicator diseases and should prompt the dermatologist to enquire about risk factors and check the HIV status of the patient.

Seborrheic Dermatitis

This condition is probably the most common skin manifestation of HIV, occurring in up to 80% of all patients (Figure 19.3). It may be widespread and severe, and is often worse in late-stage HIV disease. Red scaly patches typically affect the hair-bearing areas of the skin such as the nasolabial folds, scalp, and flexures. Treatment is that of the underlying condition using highly active antiretroviral medication. Topical corticosteroids, as well as topical or systemic imidazoles, may be helpful.

Oral-Esophageal Candidosis (Thrush)

Oral candidosis is a frequent manifestation that, in the absence of prior antibiotics, steroids, or immunosuppressive therapy, should immediately alert the clinician to the possibility of HIV infection. Severe disease may involve the posterior pharynx and esophagus, leading to dysphagia and further weight loss (Figure 19.4). Less commonly, the patient may present with erythematous candidosis, which appears as a sore red smooth shiny tongue.

Candida albicans is normally sensitive to fluconazole (50 mg daily). In cases of nonresponse, antifungal drug sensitivity to imidazoles, caspofungin, and amphotericin should be requested from the microbiology reference lab. Endoscopy with biopsy should be performed to confirm the diagnosis and exclude the main differential diagnosis of cytomegalovirus (CMV) ulceration. Multiple copathologies with different types of pathogens are not uncommon in late-stage HIV and AIDS.

Oral Hairy Leukoplakia

Oral hairy leukoplakia is seen as adherent white plaques on the lateral margin of the tongue and is virtually pathognomonic of HIV infection. It is associated with EBV infection of the oral mucosa. It may be treated with acyclovir, although this is rarely indicated. Oral hairy leukoplakia and oral candidosis in untreated patients predict progression to profound immune deficiency and development of AIDS within 1–2 years.

Molluscum Contagiosum

Molluscum contagiosum is an epidermal poxvirus infection that occurs in late-stage HIV disease. It is found in

Table 19.6 Cutaneous Manifestations of HIV Infection

Neoplasia	Kaposi sarcoma	B-cell lymphoma
	Non-Hodgkin lymphoma	Squamous cell carcinoma
	Anal carcinoma	
Infections	Herpes simplex (genital/oral/labial)	
	Herpes zoster (multidermatomal and disseminated)	
	Candidosis (oral/vulvovaginal)	
	Tinea cruris/pedis	Scabies
	Tinea versicolor/rosea	Bacillary angiomatosis
	Chancroid	Molluscum contagiosum
	Lymphogranuloma venereum	Oral hairy leukoplakia
	Syphilis	Pyomyositis
	Cryptococcosis	Histoplasmosis
	Warts (oral/genital)	Mycobacterial infections
Other eruptions	Dry skin and scalp	Onychomycosis
	Ichthyosis, xeroderma	Aphthous ulcers
	Seborrheic dermatitis	Acne
	HIV-associated gingivitis	Psoriasis
	Papular pruritic eruption (Ofuji disease)	
	Fixed drug reactions	Hypersensitivity reactions
	Black nail discoloration (zidovudine)	
	Ingrowing toenails (indinavir)	
	Hair changes	Hyperpigmentation
	Fat redistribution syndrome	

**Figure 19.3** Seborrheic dermatitis.

approximately 10% of AIDS patients. The lesions are usually 2- to 5-mm-diameter papules with a central umbilicus and tend to develop on the face, neck, and genitalia. The lesions usually disappear with treatment of the underlying HIV. Liquid nitrogen cryotherapy, topical retinoids, and cautery may be tried in cases of unsightly giant mollusca. The main differential diagnosis is disseminated cryptococcosis.

Herpes Simplex Virus Infections

Herpes simplex virus infection should be considered in any ulcerated or eroded lesion. These lesions can be painful, especially around the mouth and genitals. Recurrent, extensive, and troublesome herpes infections may occur in late-stage disease. Treatment is with high-dose acyclovir. Acyclovir resistance may develop, in which case cidofovir or foscarnet could be used as alternatives. An important differential is syphilis, which is more common in HIV. Syphilitic gumma produces painless lesions.

Varicella Zoster Virus

Shingles in an otherwise healthy person should act as an indicator for inquiry about risk factors for HIV infection. It can occur at any stage of the HIV natural history but is more frequent with failing immunity. In patients with a low CD4⁺ count (<100 cells/mm³), the eruption may affect multiple dermatomes and is often florid. Persistent, recurrent, or disseminated varicella zoster disease may also occur.

Diagnosis is confirmed by viral culture, biopsy for characteristic inclusion bodies, or electron microscopy. Treatment is with high-dose (10 mg/kg tds) IV acyclovir. Specialist help should be sought in the management of ophthalmic shingles due to the risk of permanent loss of sight. The response to treatment and the risks of postherpetic neuralgia appear to be similar to those in the HIV-negative population.

Human Papillomavirus

Human papillomavirus infection is frequent among HIV-positive men who have sex with men. The disease may be

**Figure 19.4** Orogllossal thrush.

extensive and difficult to manage. Lesions on the hands and feet (especially periungual) are also common and may attain considerable size, requiring surgery. Lesions usually improve on commencement of ART. Human papillomavirus vaccination reduces the risk of infection and oncogenic transformation.⁸

Cryptococcosis

Cutaneous cryptococcosis is caused by *Cryptococcus neoformans* (the etiological agent of cryptococcal meningitis) and occurs in very-late-stage disease ($CD4^+ < 50$ cells/mm³). Morphologically it looks similar to molluscum but more nodular patterns can develop in the severely immunosuppressed patient (Figure 19.5). A positive serum cryptococcal antigen test will usually confirm the diagnosis. Treatment is with amphotericin B plus 5-flucytosine. Most cases will require lifelong fluconazole thereafter.

Crusted Scabies

A severe variant of *Sarcoptes scabiei* infection producing a hyperkeratotic eruption (crusted scabies) may occur in advanced HIV. The infestation is often heavy, and patients are highly infectious. Uniquely in HIV infection, the face and neck can be affected. Paradoxically, the patient may not complain of severe itch. Treatment is with ivermectin. Simultaneous treatment of all close contacts and quarantine or destruction of clothing and bedding are required to prevent reinfection.

Psoriasis

Psoriasis is associated with severe flares in HIV infection, leading some to speculate on an infective etiology of this inflammatory condition. Treatment is with standard therapies. Treatment of the HIV will often improve the psoriasis.

Bacillary Angiomatosis

Bacillary angiomatosis is more common in HIV-infected individuals than are other bacterial infections such as syphilis and

infections due to *Staphylococcus aureus* (folliculitis, cellulitis, and abscesses).

Bacillary angiomatosis is due to the cat-scratch bacillus *Bartonella henselae*. Lesions range from solitary superficial red-purple lesions resembling Kaposi sarcoma to multiple subcutaneous nodules or hyperpigmented plaques. Lesions are painful and bleed readily. Disseminated infection leads to fevers, lymphadenopathy, and hepatosplenomegaly. Diagnosis is with Warthin-Starry silver staining for aggregates of intracellular bacilli.

Eosinophilic Folliculitis

Eosinophilic folliculitis, also known as pustular pruritic eruption or Ofuji disease, is more common in persons of dark skin types and increases in frequency with advancement of immunosuppression. It is associated with a raised IgE and eosinophilia. The cause is not known. Itchy follicular papules and pustules affect the face, chest, and back. Treatments are often unsatisfactory but include topical steroids, phototherapy, and antihistamines.

Kaposi Sarcoma

Kaposi sarcoma is caused by human herpesvirus 8 (HHV-8), which is transmitted primarily through saliva. It is more common in men who have sex with men (MSM). The disease may be indolent or fulminant. Rapid clinical deterioration usually ensues with visceral involvement.

It usually presents as painless purple macules, papules, nodules, and plaques affecting the limbs, face, and oral mucosa (especially the hard palate). Lesions typically follow the skin contours (Figure 19.6).



Figure 19.5 Severe nodular cutaneous cryptococcosis in an HIV-infected person.



Figure 19.6 Cutaneous Kaposi sarcoma.

The differential diagnosis includes bacillary angiomatosis and pyogenic granuloma. Prognosis depends on the CD4+ count.

There is a wide range of therapies depending on the extent of the disease. The widespread use of ART has resulted in a decline in the incidence of the disease. Combination therapy itself can result in regression of mucocutaneous lesions and even visceral disease and so is an important cornerstone of management. For refractory lesions, localized radiotherapy to lesions can result in regression of disease, including satellite lesions.⁹

ADVERSE DRUG REACTIONS

Adverse drug reactions are common in HIV and include both acute (e.g., abacavir HSR) and chronic (e.g., fat redistribution syndrome) reactions.¹⁰ Predictable reactions include drug side effects that occur in most patients who take a drug or combination of drugs. Other drug reactions previously thought to be idiosyncratic are now known to be genetically determined.^{11,12}

Nevirapine rash is a common side effect that begins within 2–4 weeks of starting this treatment. If severe, it may result in SJS. Pharmacogenetic screening is now part of routine clinical practice in HIV medicine since the introduction of HLA compatibility testing prior to initiation of abacavir.¹³

Abacavir Hypersensitivity Reaction

Abacavir (Ziagen) is a nucleoside analogue reverse transcriptase inhibitor licensed for the treatment of HIV. It is frequently used as a first-line drug due to its once-daily formulation and favorable lipid (fat redistribution syndrome) profile. It is an active component of coformulations Kivexa (with lamivudine), Trizivir (with lamivudine plus zidovudine), and Triumeq (Kivexa plus dolutegravir). Abacavir HSR occurs in 5%–8% of patients during the 6 weeks of therapy, with a median onset of 11 days.¹⁴ It usually presents with fever (80%) and rash (70%). Less common symptoms include nausea, vomiting, pruritus, malaise, diarrhea, abdominal pain, and fatigue. Numbness of the skin; puffiness of the throat, face, and neck; swollen glands; conjunctivitis; mouth ulcers; and low blood pressure may also occur.

Symptoms of the HSR to abacavir are nonspecific and may mimic influenza, the key difference being the presence of GI symptoms with abacavir. Symptoms worsen with continued use of the drug. Rapid reversal of symptoms occurs on discontinuation of abacavir.

An abacavir HSR may be life threatening; therefore, all patients prescribed this should be made familiar with the symptoms and should know to notify their doctor immediately if they develop any of these. More severe and even fatal reactions have been reported in patients rechallenged with abacavir after stopping the drug. Subsequent rechallenge with abacavir is therefore absolutely contraindicated.

Abacavir hypersensitivity is strongly associated with an HLA-B*5701 allele. Testing for the HLA B*5701 haplotype reduced the incidence of HSRs to zero in a randomized trial of nearly 2000 patients.¹³ All patients should therefore be screened for this allele prior to commencing therapy.

The HLA B*5701 allele appears to be more common in white Caucasians and least common in black Africans infected with HIV (and in whom dermatitis is often more difficult to

distinguish). It is recommended that genetic testing should be routine for people of all ethnicities to reduce the instances of misdiagnosis of hypersensitivity in which abacavir is inappropriately withdrawn from patients who could have benefited from it.

Immune Restoration Inflammatory Syndrome

Immune restoration inflammatory syndrome (IRIS) is an adverse consequence of the restoration of pathogen-specific immune responses in HIV-infected patients during the initial months of ART. The inflammatory syndrome reflects the restoration of a previously impotent immune system as it mounts an excessive response against organisms that were already present, but dormant, in the body.¹⁵

The immune restoration can have various manifestations, including lymph-node inflammation associated with *Mycobacterium avium-intracellulare* complex (Figure 19.7); eye inflammation (uveitis or vitreitis) associated with CMV; worsening of tuberculosis, cryptococcosis, or toxoplasmosis symptoms; and elevated liver enzymes associated with hepatitis B or C coinfection.

The incidence of IRIS is greatest in patients with advanced immune suppression (CD4+ count <100 cells/mm³) at the start of therapy. Immune restoration reactions are associated with larger viral load reductions (2.5 log or greater) or CD4+ cell increases after starting HAART. Starting an anti-HIV treatment with a combination that included a ritonavir-boosted protease inhibitor was also associated with an increased risk of IRIS.⁹

Because flare-ups indicate improvement of immune function following antiretroviral therapy, antiretroviral therapy is continued in all but the most serious cases. Even then it is usually only stopped temporarily until the patient's condition has stabilized. Antiinflammatory medications may help decrease symptoms during the intense inflammatory phase, but routine use of corticosteroid therapy is generally avoided. There have been anecdotal reports of successful management of reactions using pentoxifylline, thalidomide, and the asthma medication montelukast. Most case reactions resolve on their own without any additional treatment. Specific medical or surgical interventions may be warranted in case of threatened neurologic or respiratory compromise.^{16,17}



Figure 19.7 Suppurative mycobacterial adenopathy as an immune restoration inflammatory syndrome reaction following commencement of highly active antiretroviral therapy.

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Graft versus host diseases

Jasna Lipozenčić and Ronni Wolf

Graft-versus-host disease (GVHD) represents one of the most frequent complications and causes of morbidity in patients who undergo allogeneic hematopoietic cell transplantation for hematologic malignancies.

GVHD is classified into acute and chronic forms based on clinical manifestations.^{1,2} The skin is a major target organ for both acute and chronic graft-versus-host disease (GVHD) after stem cell transplantation (SCT).²

Although SCT is a life-saving measure and the treatment of choice for many patients with various hematologic malignancies, a high incidence of complications and a transplantation-associated mortality approximately 30% are to be expected. GVHD is the major cause of morbidity and mortality at any time following SCT. The acute form occurs during the first 100 days after transplantation in up to 50% of graft recipients, whereas chronic GVHD develops in approximately 30%–50% usually within 100–500 days following allogeneic SCT. Target organs in GVHD can be all of those with lymphoid cells, as well as epithelial structures, especially the skin, liver, gastrointestinal (GI) tract, lung, eyes, and neuromuscular system. Early diagnosis of GVHD can be difficult, because drug reactions, viral infections, and cutaneous reactions to radiation therapy may have similar clinical similarities. Histologic findings of GVHD correlate poorly with clinical severity of the disease and have a limited role in predicting disease stage and progression.^{3,4} The skin manifestations, histopathologic features, prophylaxis, and therapy of acute and chronic GVHD are presented in this chapter.

PATHOPHYSIOLOGY OF GVHD

GVHD is the result of a complex interaction of associative inflammation, endotoxicity, and activation of alloreactive cells. Cytotoxic donor T lymphocytes are mediators and effectors in GVHD. Proinflammatory cytokines in the cells of the donor, and the recipient play an important role in the pathogenesis of GVHD. In acute GVHD, there are increased serum concentrations of tumor necrosis factor- α (TNF- α), interferon- γ (IFN- γ), interleukin 1 (IL-1), IL-2, and IL-6, but they are not specific for GVHD because bacterial infections show similar findings. The only correlation has been found between elevated IL-2 receptor (IL-2R) and severe GVHD.^{5,6} Prophylactic administration of monoclonal anti-TNF- α antibodies in a patient with histocompatibility leukocyte antigen (HLA)-identical SCT in twins significantly alleviated acute GVHD.

GVHD is in direct correlation with HLA incompatibility between donor and recipient.⁷ Even in HLA-identical related SCT without prophylactic immunosuppression, GVHD occurs in 30%–50% of cases and has a severe course in 10%–20% of cases due to so-called HLA minor antigens.⁸ HLA incompatibility between donors and patients increases the incidence of GVHD. The age of patients, as well as difference in sex between

donor and recipient, are also risk factors, when there are two different HLA antigens and Y-chromosome-associated minor antigens.^{2,4} In HLA-identical SCT, the incidence of GVHD is less than 25% in patients younger than 30 years with acute GVHD, but this number rises to 80% in patients older than 50 years.⁹ The incidence of chronic GVHD is also higher in adults than in children.⁴

HLA incompatibility, age, and gender are not the only factors responsible for GVHD.¹⁰ A three-phase model may explain the pathophysiology of GVHD.⁴ Phase I is “toxic” and lasts for approximately 60 days, whereas phase II begins with “lichenoid” manifestations before the 30th day and lasts until approximately the 100th day.⁴

There is interaction between different cell populations in both donor and recipient, as well as between mediators of inflammation, and the result is cell death (apoptosis) in target organs of GVHD.² Chronic GVHD often develops from acute GVHD through costimulation of cytokine production, and end-cell apoptosis through endotoxins is intensified. In this phase, there is hypersensitivity of macrophages through Th1-cytokine (INF- γ) stimulation. In acute GVHD, there is activation of Th1 cytokines with the production of inflammatory cytokines (TNF- α , IL-1, and IL-6), accompanied by organ-specific destruction and Th1 activation of cytotoxic T-lymphocytes natural killer, TNF- α .^{2,11,4}

Risk factors for GVHD are genetic polymorphism in the promoter region of inflammatory (TNF- α) and antiinflammatory (IL-10) cytokines. In chronic GVHD, there is the added risk factor of a former acute GVHD and the subsequent activation of Th2 cells and cytokine production. The chronicity of GVHD is due to alloreactive T cells having increased the production of IL-4 or IFN- γ , which induce collagen synthesis through fibroblasts.⁴

Acute GVHD

Acute GVHD begins 2–6 weeks after transplantation (median 3 weeks). In one study, GVHD took place after allogeneic SCT in 35% of patients with HLA-identical donors, and the disease course was severe in 10%–20% of these cases (erythroderma, toxic epidermolysis).⁴ Acute GVHD is manifested in the skin (maculopapular eruption), the liver (cholestatic hyperbilirubinemia and jaundice), and the GI tract (nausea, diarrhea, and vomiting), as well as the lymphatic system, bone marrow, and the mucosa of the mouth and respiratory system. Development of “hyperacute” GVHD has been described as occurring 7–14 days after SCT.⁹

SKIN MANIFESTATIONS OF ACUTE GVHD

The skin is the target organ of acute GVHD in more than 90% of cases. Early manifestations of acute GVHD include generalized

pruritus, dysesthesia, painful palms and soles, or edema and erythema of the ears.¹² A maculopapular eruption first appears on the face, palms, and soles, followed by the shoulders and abdomen and then the whole body. These eruptions cannot be distinguished from a drug eruption or viral exanthema, either clinically or histologically. Exanthemas are variable and can be purpuric, follicular, morbilliform, or scarlatiniform. Perifollicular papular reactions indicate progression to a severe course, being characteristic of GVHD.⁴

Erythema on the palms, soles, and ears is typical in GVHD. Exanthemas with progression to erythroderma and blisters with a positive Nikolsky phenomenon are signs of a severe course. The most severe cases are those with bullous GVHD that include toxic epidermal skin and mucosal necrolysis and septicemia. Toxic epidermal necrolysis (TEN) has been reported in 6% of cases with very high mortality.⁴ In this phase of GVHD, it is not easy to distinguish the epidermal necrolysis of SCT from that of drug-induced TEN. Hyperacute GVHD with TEN has been reported as early as 8 days after bone marrow transplant.¹⁰

Mucosal reactions present as xerostomia, symptomatic of salivary gland dysfunction and pain upon eating, as well as mucosal hypersensitivity. Oral mucosal reactions in acute GVHD can appear as fine papular white lesions, whitish lichenoid-reticular signs, or desquamative erosive changes.

In the progressive stage of acute GVHD, there are fingernail changes with periungual erythemas, hyperkeratosis, onycholysis, pigmentations, and hemorrhage of the nail plates. Generalized erythroderma with bullous formation is in the late stage 4 of the grading system with severe abdominal pain with or without ileus.¹³

EXTRACUTANEOUS MANIFESTATIONS

The liver and the GI tract can be target organs after allogeneic SCT.¹⁴ GI manifestations are present in 30%–50% of cases of acute GVHD.¹⁴ They appear early or shortly after the skin manifestations and include diarrhea, vomiting, anorexia, malabsorption, abdominal pain, ileus, and colon hematuria, all of which are signs of a severe course. Liver disorders (bilirubin, alkaline phosphatase, γ -glutamyltranspeptidase) with hepatomegaly are the second most prevalent manifestations after those of the skin and are found in 40%–60% of cases.^{4,10}

CLINICAL STAGES OF ACUTE GVHD

Acute GVHD severity has been graded by pattern of organ involvement and clinical performance status using a system introduced more than 30 years ago.¹⁵ According to this system, acute GVHD severity is graded by clinical stage and percentage of skin lesions, GI disorders, volume of diarrhea (mL/day), and value of bilirubin.^{4,15} For example, stage I is characterized by maculopapular exanthema (<25% body size), bilirubin 2–3 mg/dL, and diarrhea of 500–100 mL/day, whereas stage IV is characterized by bullous manifestations with TEN in the skin, bilirubin >15 mg/dL, and pain or ileus.^{4,15,16} In acute GVHD, the “grade” survival is correlated with GVHD severity in grade (specifically, >90% survival in grade I, ~60% in grades II and III, and 0% in grade IV).

The International Bone Marrow Transplant Registry has adopted a new severity index for grading acute GVHD, based on objective parameters of target organs. It has been proposed

that the Severity Index enhances design and interpretation of clinical trials in the current era of allogeneic blood and bone marrow transplantation.^{13,16}

HISTOLOGIC CHANGES OF ACUTE GVHD

Prophylaxis depends on the degree of severity of acute GVHD and on histologic changes resulting from GVHD. The dynamism of GVHD makes the histologic picture unstable, and it characteristically changes during the course of illness due to its being influenced by many other factors. Histologic findings of the skin in early acute GVHD show focal basal cell degeneration of the epidermis and sometimes sparse perivascular lymphocytic infiltration in the upper part of the dermis. In the late acute phase, there is a hypersensitivity reaction and activation of endothelial cells as well as penetration of T cells into the papillary dermis. The clinical signs include cytotoxic folliculitis and “satellite necrosis” due to the presence of T cells in the papillary dermis, lymphocytes in the epidermis, and hair follicles, as well as necrosis of keratinocytes/apoptosis or necrosis.⁴

Histologic changes in acute GVHD have been described as grade I (vacuolization of basal cells of inflamed lymphocyte infiltrate in the upper part of the dermis or epidermis), grade II (dyskeratosis of some keratinocytes, exocytosis of lymphocytes around necrotic keratinocytes in the epidermis [“satellite phenomenon”]), grade III (the beginning of late signs in the basal membrane zone with sparse necrosis in the epidermis), and grade IV (complete depletion of necrotic epidermis) (Figure 20.1).^{4,15}

These histopathologic changes are not specific to GVHD, and similar ones can be found in viral exanthems, drug eruptions, and after chemotherapy. This is the reason for the need for optimal timing for skin biopsies: 24–48 hours after exanthema,

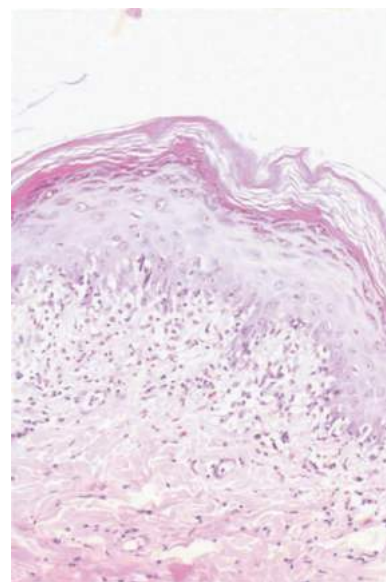


Figure 20.1 Graft-versus-host disease, acute stage, stage II histologic feature: Rare subepidermal infiltrate of lymphocytes (with sparse lymphocytes in lower part of the epidermis), hydrops degeneration of the basal cell layer, and “satellite” cell necrosis. H&E $\times 240$. (Photo courtesy of Ivan Dobric, MD, PhD, Zagreb, Croatia.)

before administering GVHD therapy and repeated biopsies in the early phase of acute GVHD, with paraffin block serial slices for focal GVHD with mostly follicular involvement.¹⁴

DIFFERENTIAL DIAGNOSIS

The clinical manifestations of viral exanthema and drug eruption are similar to dermal manifestations in the initial phase of GVHD. Skin bullous changes take place after total beam radiotherapy, accompanied by palmo-plantar pain and stomatitis some weeks later; thus, it is imperative that the diagnosis is clear-cut, that clinical examinations are repeated, that biopsies are taken, and that microbiologic findings are available. Increased values of liver enzymes or GI disorders can appear concomitantly with acute GVHD. Another cause for consideration includes the side effects of immunosuppressive therapy.

Physicians need to recognize atypical early skin involvement in acute GVHD in patients after SCT, so that they can promptly initiate appropriate treatment.¹⁷ There is a suggestion of an association between acquired ichthyosis with GVHD.¹⁸ Epidermodysplasia verruciformis in the setting of GVHD after SCT has also been described.¹⁹

PROGNOSIS OF ACUTE GVHD

The morbidity and mortality rates that determine prognosis in progressive acute GVHD are high after SCT. Whereas the prognosis is good in cases of isolated skin GVHD or GVHD grade II when response to the first course of therapy is positive, it is grave in patients with refractory or severe GVHD. Even patients with GVHD grade II–IV have a low mortality rate, if they react to initial therapy with complete remission. Fewer than 50% of patients with acute grade II–IV GVHD have long-term survival, so early diagnosis and therapy are essential. The most prevalent causes of death are infections, bleeding, and suppression of liver function.

Chronic GVHD

Chronic GVHD (100–500 days after SCT) is a multisystem disease, and between 30% and 50% allogeneic transplantation patients develop it.^{1,4} The major risk factor for chronic GVHD is acute GVHD. Chronic GVHD can be either subclinical or clinical and either limited or extensive. Skin changes are local in 20% of cases and generalized in 80%. They can be progressive (32%) following acute GVHD, as well as *de novo* (30%). Chronic GVHD can appear after ultraviolet radiation, trauma, or herpes zoster.⁴

SKIN MANIFESTATION OF CHRONIC GVHD

Skin is the most frequently targeted organ in chronic GVHD.^{4,14} The initial changes that take place, together with other early manifestations of chronic GVHD, include persistent face erythema with marked pigmentation, mouth dryness (xerostomia, ulcers, restrictions of mouth opening from sclerosis), and sensitivity to spicy food that can be associated with oral pain.^{4,13} Because skin changes can appear rapidly after sun exposure, sunscreens are vital for these patients. One-fifth of them have a localized skin form of GVHD and rarely exhibit liver symptoms. The dermal expression is mostly lichen ruber planus (LRP), lichen sclerosus et atrophicus, or skin lesions linear to

or along Blaschko lines⁴; circumscribed scleroderma is rare (3%). Generalized forms seen in disseminated GVHD are erythema, desquamation, telangiectasia, and pigmentation disorder. There are two chronic disseminated GVHD forms: lichenoid and sclerodermiform. The former is similar to LRP and characterized by livid-brown papillae on the extremities (Figure 20.2). They are often present periorbitally on the ears, hands, and soles, and lichenoid papular lesions are sometimes localized in the hair follicles. Generalized skin lesions and erythroderma are rare. Postinflammatory hyperpigmentation may appear after regression of the lesions, whereas hypopigmentation is uncommon. Pityriasis rosacea-like lesions in GVHD with rapid regression have been described, as well.⁴

In addition to LRP, mucosal mouth lesions in chronic GVHD include Wickham striae, erosions, ulcerations or leukoplakia, painful erosions, and xerophthalmia, similar to that found in the sicca syndrome. Nail disturbances are seen in approximately 40% of patients, and they range from onycholysis, pterygium, and atrophy to total nail loss.

Sweat glands often show a disturbance of function until dehydration. Other changes include pigment loss in hair, cicatricial alopecia, and poikiloderma with alopecia in sclerodermiform form, as well as vitiligo.

Sclerodermiform GVHD is a severe sequela of chronic GVHD that often occurs before LRP GVHD. It is a type of sclerosis of the dermis with localized morphea and generalized skin lesions that include contractures and ulcers with possible superinfections. This form is associated with HLA-A1-B1 and B2. Fasciitis is rare in chronic GVHD, as are eosinophilic fasciitis and cellulitis.⁴

Extracutaneous manifestations in chronic GVHD represent severe multisystem disease with involvement of the liver (jaundice, transaminitis) (30%), GI tract (anorexia, weight loss, esophageal web or strictures; diarrhea approximately 30%), lung (dyspnea, bronchitis), eyes (conjunctivitis, keratitis), and



Figure 20.2 Graft-versus-host disease, chronic stage, lichenoid form. Papular exanthema on the trunk. (Photo courtesy of Ivan Dobric, MD, PhD, Zagreb, Croatia.)

the neuromuscular system. Glomerulonephritis and arthritis are uncommon.¹³ According to National Institutes of Health Consensus Criteria, there are similar clinical signs and symptoms.¹²

CLINICAL STAGES OF CHRONIC GVHD

Chronic GVHD can start subclinically (~30%) or display clinical signs and symptoms (70%) that are either localized (20%) or generalized (80%).⁴ The traditional clinical grading system⁹ is divided into three categories: subclinical grade I without evidence of GVHD but with positive histologic findings; clinical grade II with limited disorders and localized skin lesion and liver dysfunction; and clinical grade III with extensive skin lesions, liver dysfunction, and hair loss, accompanied by histologic evidence of aggressive hepatitis, necrotic lesions, and cirrhosis in addition to other organ involvement, such as eyes, oral mucosa, colon, and lung.^{4,9,12}

HISTOLOGIC CHANGES IN CHRONIC GVHD

As in acute GVHD, there are four histologic forms⁴: (1) acanthosis, parakeratosis, hyperkeratosis, and hypergranulosis of the epidermis; (2) lichenoid GVHD with lichenoid infiltrate and melanophages, eosinophils, and plasma cells in the papillary dermis (Figure 20.3); (3) sclerodermiform GVHD with homogeneous and swollen bundles of collagen and loss of appendages (Figure 20.4); and (4) atrophy of the epidermis (late phase). The lupus band test is positive in 86% of biopsies in chronic GVHD. There are no specific histologic parameters to differentiate between acute and chronic GVHD. Autoreactive clones of T cells have been identified in animal models of chronic GVHD that are specific for common antigens shared between host and

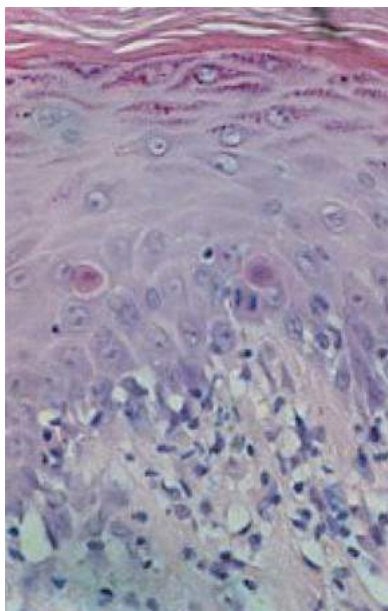


Figure 20.3 Graft-versus-host disease, chronic stage lichenoid form, histologic feature: Hypergranulosis and rare subepidermal bordered infiltrate of lymphocytes. H&E ×200. (Photo courtesy of Ivan Dobric, MD, PhD, Zagreb, Croatia.)

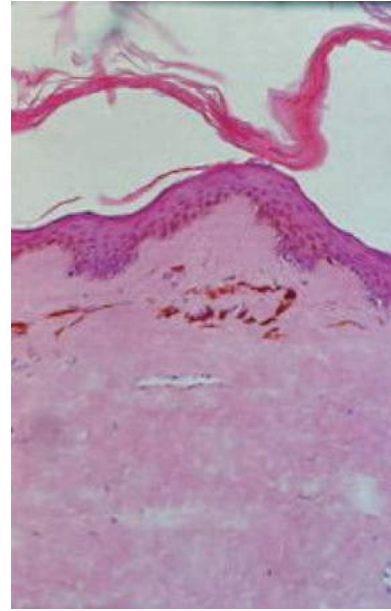


Figure 20.4 Graft-versus-host disease, chronic stage, scleroderma form, histologic feature: acellular dermis with swollen bundles of collagen and loss of structure in interfascicular space with melanophages, subepidermally. H&E ×200. (Photo courtesy of Ivan Dobric, MD, PhD, Zagreb, Croatia.)

donor.¹² These pathogenic T cells can then escape tolerance mechanisms.¹² Recent data have suggested an involvement of Th-1 and Th-17 cells, as well as an altered regulatory T-cell homeostasis.¹¹ An increasing number of reports also suggest a key role of B cells.¹¹

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of chronic GVHD includes circumscribed and systemic scleroderma, lichenoid drug eruption, lupus erythematosus, pityriasis rosea, eosinophil fasciitis, Sjögren syndrome, rheumatoid arthritis, primary biliary cirrhosis, hyperpigmentation of the palms and soles, contact dermatitis, staphylococcal scaled skin syndrome, toxic shock syndrome, and eruption of lymphocyte recovery.¹⁶

PROGNOSIS OF CHRONIC GVHD

Prognosis is more favorable, if the disease is limited to skin or liver involvement. In cases of more extensive disease in which multiple organs are affected and there is inadequate response to therapy, 80% of the patients will die. The prognosis of sclerodermiform GVHD is grave. Morbidity and mortality are highest in patients, whose disease process had begun with acute GVHD and lowest in patients who had not undergone acute GVHD previously. The most prevalent causes of death are bacterial and viral infections.

PROPHYLAXIS AND THERAPY FOR GVHD

The most important factors in primary prophylaxis are choice of donors and histocompatibility. Drug prophylaxis (see below) is also essential.

Acute GVHD

Basic prophylaxis begins on the day of transplantation. It is initially intravenous and is followed by 6 months of oral cyclosporine A (CSA) in combination with methotrexate (MTX) or systemic corticosteroids instead of MTX. Tacrolimus is currently preferred over cyclosporine, and some studies favor mycophenolate mofetil over MTX.⁴ In vitro physical separation of immunocompetent T cells or antilymphocyte or antithymocyte serum, as in vivo T-cell reducers, is used as well. Basic prophylaxis can decrease the incidence of acute GVHD but not of chronic GVHD. The therapeutic regimen for corticosteroid-resistant cases consists of cyclophosphamide, antithymocyte globulin, antilymphocyte globulin, pentostatin, or monoclonal antibody against T lymphocytes or against immunosystem mediators (IL-2R, TNF- α).⁴ The addition of other immunosuppressive therapeutic agents in GVHD comprises a risk for infections (fungal, viral), as well as associated Epstein-Barr virus lymphomas. Supportive therapy is fundamental for acute and chronic GVHD infections.⁴

Chronic GVHD

Skin lesions are the first manifestations in 90% of GVHD cases, but all target organs must be evaluated before therapy is administered. CSA and corticosteroids comprise the initial therapy. When an alternative therapy is needed due to resistance, mycophenolate mofetil with tacrolimus is one option, having shown a good effect in 50% of patients with drug-resistant chronic GVHD.⁴ In isolated skin GVHD, photochemotherapy with 8-methoxypsoralen is effective, as is D-penicillamine and azathioprine or high-dose thalidomide. Acitretin and clofazimine can be given for sclerodermiform GVHD resistant to etretinate. Extracorporeal photopheresis is also effective and has fewer side effects. Ultraviolet B phototherapy is considered adjuvant therapy in chronic GVHD.^{4,16} Causal therapy is not yet available. Known side effects of therapy associated with immunosuppression involve the kidney and lead to liver and bone marrow impairment, as well as to tumors. The use of sunscreens is an important supplement to medication. Therapy for GVHD patients should be in the hands of hematologists and dermatologists.

MANAGEMENT OF GVHD

The influence of nonmyeloablative and ablative conditioning regimens on the occurrence of acute and chronic GVHD was recently evaluated in 137 patients.²⁰ Myeloablative regimens included intravenous bisulfan/cyclophosphamide ($n = 45$) and fludarabine/melphalan ($n = 29$). The nonmyeloablative group ($n = 63$) received fludarabine/idarubicin/cytarabine, cisplatin/fludarabine/idarubicin, and fludarabine/cyclophosphamide. The actuarial rate of grade II-IV acute GVHD was significantly higher in patients receiving ablative regimens (36%) compared with the nonmyeloablative group (12%). The cumulative incidence of chronic GVHD was higher in the ablative group (40%) compared with the nonmyeloablative group (14%).²⁰

The time of onset of GVHD and survival rate were analyzed in 395 patients with hematologic malignancies who underwent a nonmyeloablative regimen of 2 Gy total-body irradiation with or without fludarabine followed by post-grafting immunosuppression with mycophenolate mofetil and cyclosporine. The cumulative incidences of grades II-IV

acute GVHD and extensive chronic GVHD were 45% and 47%, respectively. High-dose corticosteroid treatment for acute or chronic GVHD was started at a median of 79 days and 30 days after transplantation, respectively.²¹ If the donors were related, the cumulative incidence of nonrelapse mortality among patients with GVHD was 55% at 4 years, when prednisone was started before day 50. The authors concluded that patients with early onset GVHD after nonmyeloablative SCT from HLA-identical related donors might benefit from intensified primary immunosuppressive treatment.²¹ The decision to treat immediately for GVHD without performing a skin biopsy provided the best patient outcomes.²² When the prevalence of GVHD was 50% or higher (typical for allogeneic SCT), the best outcomes were obtained with treatment for GVHD and no skin biopsy. In populations with a prevalence of GVHD of 30% or less, obtaining a skin biopsy specimen to guide treatment was predicted to provide the best patient outcome.²² One report showed that a better therapeutic approach would be the reduction of immunosuppression to allow the patient's immune system the opportunity to reject the allograft donor T cells. The patients, who responded to withdrawal of immunosuppression, had a later onset of symptoms and a lower level of donor CD3+ T cells at the start of treatment.²³ Other investigators have suggested that the patients with "composite" skin GVHD may benefit from an earlier, more aggressive immunosuppressive interventional strategy.²⁴ Imatinib has shown a major impact on chronic myeloid leukemia treatment strategies. GVHD involving the skin, liver, and digestive tract has been described in the syngeneic transplant setting, either with or without administration of prophylactic cyclosporine: Complete remission was achieved with imatinib.^{13,25} Some benefit has occurred with small phase II trials with rituximab, an antiCD20 chimeric monoclonal antibody for use in refractory chronic GVHD, as well as with antibodies activating the platelet-derived growth factor receptor pathway. Imatinib is successful biological during the past three decades, but no effective prophylaxis regimen currently exists for chronic GVHD.¹³

CONCLUSIONS

GVHD is a devastating complication following SCT, and the prevention of GVHD is of the highest priority. Future strategies to identify the best possible transplant donor will incorporate HLA and non-HLA genetic factors. Management of these patients should be multidisciplinary and involve hematologists and dermatologists. There is no known therapy for the causes of GVHD nor means of avoiding the side effects of immunosuppression that are often present in affected patients. Management is determined according to the stage of GVHD, and early diagnosis is of the essence. Identification of biomarkers for GVHD with diagnostic and prognostic significance will improve the management of GVHD in the future.

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Erythroderma/exfoliative dermatitis

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Erythroderma is one of the most important diseases to confront the dermatologist as an emergency. An extreme state of skin irritation resulting in extensive erythema and/or scaling of the body in several skin disorders may ultimately culminate in erythroderma/exfoliative dermatitis. Largely, it is a secondary process; therefore, determining its cause is necessary for appropriate diagnosis and therapy.¹ Its clinical pattern is fascinating and has been the subject of detailed studies: Its changing scenario in various age groups,^{2,3} its presentation postoperatively, and its occurrence in human immunodeficiency virus (HIV)-positive individuals are vivid indicators.

Several factors may be responsible for the causation of this extensive skin disorder: a detailed outline of a patient's history to elicit possible triggering events, namely, infection, drug ingestion, topical application of medicaments, and sun/ultraviolet light exposure, among other factors. It is also challenging to manage the condition, because the intricate process puts an extensive strain on an already compromised body system.^{1,2,4,5} In addition, the original dermatosis may be masked by extensive erythema/scaling, thus making it difficult to obtain a clear-cut diagnosis. Its clinical expression in neonates/infants and children poses a serious emergent challenge for its life-threatening overture.^{6,7}

DEFINITION

Erythroderma and exfoliative dermatitis are largely synonymous; however, erythroderma is the preferred term^{1,8} and is currently in vogue. The former is characterized by extensive and pronounced erythema, coupled with perceptible scaling, whereas the latter presents widespread erythema and marked scaling. (This distinction often cannot be made in more recent reports.) Accordingly, 90% or more skin-surface involvement and widespread scaling is considered as a salient prerequisite to make a clinical diagnosis of erythroderma/exfoliative dermatitis.¹ The extensive cutaneous capillary dilation spreads across the body, leading to widespread exfoliation of the epidermis.⁹ Some disorders in infants may initially be localized and then eventually develop into extensive erythema.¹⁰

INCIDENCE

It is hard to obtain a precise incidence for erythroderma/exfoliative dermatitis, as most reports are retrospective and do not address the issue of overall incidence. In surveys from India and the Netherlands, the annual incidence was recorded as variable at 0.9–35 per 100,000 skin patients.^{1,11} A large number of patients were HIV positive, where a drug reaction was the most common cause, and men were affected two to three times more frequently.⁵ In a systematic review the cutaneous adverse drug

reactions were evaluated in 3671 patients, erythroderma and mortality rates were 1.01% and 3.57%, respectively; whereas¹² another group found the erythroderma rate to be 7.54% in all cutaneous adverse drug reactions.¹³

The incidence, as a function of age, is usually variable, and any age group may be affected; however, affected (excluding hereditary disorders/atopic dermatitis) patients are usually older than 45 years,¹ with a mean age 42–61 years and an average age of onset of 55 years.^{14,15} It is more common among men than women, the reported male-to-female ratios varying between 2:1 and 4:1.¹⁶ The condition is somewhat rare in children, as might be expected, with a reported prevalence of nearly 0.1% among the pediatric population admitted to dermatology clinics.^{17,18}

A sample of 80 patients with erythroderma contained only seven of the pediatric age group, of which only three belonged to 0–3 years and the other four to 4–13 years, equating to an incidence of 8.8%.^{1,19} The boy-to-girl ratio was approximately equal, whereas age at onset varied according to causative factors.

ETIOLOGY

Erythroderma is normally associated with a set of symptoms and signs that may appear nonspecific or related to other diseases; however, the combination of these different clinical manifestations may, when taken together, help with the identification of the condition and the underlying etiology.¹⁶

Erythroderma may embrace or be caused mainly by certain preexisting dermatoses, drugs, malignancy, and miscellaneous/idiopathic disorders.^{1,10} The etiologic factors in both the pediatric and adult populations are shown in Tables 21.1 through 21.3.

Several dermatologic disorders or their therapy can result in erythroderma (Tables 21.1 and 21.2), where it is frequently caused by the exacerbation of a previously existing inflammatory dermatosis, such as atopic dermatitis and psoriasis.^{14,20–22} Among psoriasis patients, erythroderma may be triggered by a variety of factors, including medication (e.g., antimalarial drugs or lithium), systemic diseases, immunosuppressants, HIV infection, topical irritant agents, phototherapy burns, or emotional stress.²³

Hypersensitivity reactions to drugs is the second most commonly reported cause of erythroderma, accounting for nearly 20% of all cases. A broad range of pharmaceuticals are known to trigger erythroderma, ranging from penicillins, sulfonamides, carbamazepine, phenytoin, to allopurinol.²¹

Lymphomas in general and T-cell lymphoma (comprising mycosis fungoides and Sézary syndrome) are often reported to present as erythroderma. Erythroderma may develop before, during, or after the development of T-cell lymphomas and may initially appear as benign erythroderma. Immunophenotypic

Table 21.1 Etiology: Erythroderma/Exfoliative Dermatitis in Children

Cause(s)	Disease(s)/Syndrome(s)
Cutaneous disorders	Atopic dermatitis
	Psoriasis vulgaris
	Seborrheic dermatitis
	Pityriasis rubra pilaris (PRP)
	Ichthyosis—harlequin, lamellar, bullous
Immunologic disorders	Diffuse cutaneous mastocytosis
	Omenn syndrome
	Graft versus host disease
	Hypogammaglobulinemia
	DiGeorge syndrome
Metabolic/nutrition disorders	Leiner disease
	Sjogren-Larsson syndrome
	Holocarboxylase synthetase deficiency
	Kwashiorkor
	Acrodermatitis enteropathica
Infections	Cystic fibrosis
	Amino acid disorders
	Staphylococcal scalded skin syndrome
	Scarlet fever
	Toxic shock syndrome
Drug reactions	Neonatal candidosis
	Syphilis
	Crusted scabies
	Drug-induced erythroderma
	DRESS
Part component of various syndrome	Toxic epidermal necrolysis
	Netherton syndrome
	Sjögren-Larsson syndrome
	Keratitis-ichthyosis-deafness syndrome
	Ectodermal dysplasias
Malignancies	Neutral lipid storage disease with ichthyosis
	Conradi-Hünemann syndrome
	Trichothiodystrophy
	Cutaneous T-cell lymphoma

Source: Data adapted from Sehgal VN, Srivastava G, Sardana K. *Int J Dermatol* 2004;43:39–47.

Table 21.2 Dermatoses Frequently Resulting in Exfoliative Dermatitis in Adults

Common	Uncommon
Psoriasis	Candidosis
Airborne contact dermatitis	Mastocytosis
Seborrheic dermatitis	Lichen planus
Atopic dermatitis	Reiter syndrome
Dermatophytosis	Toxic epidermal necrolysis
Staphylococcal scalded skin syndrome	Diffuse/erythrodermic mastocytosis
Phytophotodermatitis	Sarcoidosis
Photosensitive dermatitis	Pemphigoid
Pityriasis rubra pilaris (PRP)	Lupus erythematosus
Pemphigus foliaceus	Crusted (Norwegian) scabies
Stasis dermatitis	Ichthyosiform erythroderma

Source: Data adapted from Sehgal VN, Srivastava G, Sardana K. *Int J Dermatol* 2004;43:39–47.

examination, involving advanced antibody panels, may be necessary to distinguish malignancy-associated erythrodermas from benign erythroderma.^{24,25}

Other solid organ or reticuloendothelial tumors, lymphomas, or leukemias appear to be rarely involved in the causation of erythroderma.^{4,13,14,26–29}

Less commonly reported causes of erythroderma in the adult population include infections, connective tissue diseases, malignant tumors, immunobullous disease, and pityriasis rubra pilaris (PRP). Reticuloendothelial and hematologic malignancies, as well as solid malignancies in organs, may also trigger erythroderma³⁰; the causative disorders can be masked due to generalized erythema and/or scaling.^{20,21}

In all age groups from infants to the elderly, various other conditions, such as acquired immune deficiency syndrome (AIDS), hepatitis, graft-versus-host disease (GVHD), irradiation, the Omenn syndrome, the papuloerythroderma of Ofuji, and a variety of cutaneous diseases, may also be responsible for the appearance of erythroderma.^{1,15,31–33} These underlying diseases can sometimes be concealed or masked due to generalized scaling or erythema; for this reason, careful and thorough examination is necessary to identify them.^{22,23} The other cutaneous diseases implicated in the development of erythroderma are summarized in the section “Clinical Presentation/Connotation.”

The etiologic factors involved in the development of erythroderma in newborns and infants include infections (such as syphilis, congenital cutaneous candidosis, and staphylococcal scalded-skin syndrome), dermatoses (such as seborrheic dermatitis, psoriasis, and atopic dermatitis), and medication. Among younger children, the most common cause of erythroderma is an underlying dermatosis. In addition, a number of congenital diseases, such as primary immunodeficiencies, bullous and nonbullous congenital ichthyosiform erythroderma, Netherton syndrome, and ichthyoses, are also known to be possible causative factors of erythroderma in this patient population.^{30–34} In a significant study comprising neonatal and infantile (up to 1 year) erythroderma, the composition was 30% in an immunodeficiency state, 24% in ichthyosis, 18% in Netherton syndrome, 20% had papulosquamous/eczematous dermatoses, and a further 8% were idiopathic.²¹

Despite the best endeavors, approximately 20%–30% of ED cases remain without a clear-cut etiology; such disorders are classified as “idiopathic” and are often referred to as “red man syndrome,” which is also used to describe an infusion reaction to vancomycin.^{14,30,35} Comparison of this group with the erythrodermic patient group showed that lymphadenopathy and peripheral edema were both more common than other types of erythroderma, and that hypothermia was observed more frequently than hyperthermia.³⁶ A sustained effort during the course of follow-up may lead to the precise definition of the etiology.^{1,19}

PATHOGENESIS

The pathogenesis of the erythroderma/exfoliative dermatitis appears complex. It is surmised that the condition develops secondary to an intricate interaction of cytokines and cellular adhesion molecules; interleukin 1, 2, and 8; intercellular adhesion molecule 1; and the tumor necrotic factor.^{26,27,30,36} In patients where erythroderma is secondary to a dermatitis or psoriasis, as well as in Sézary syndrome patients, a higher level of such adhesion molecules as E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 are often identified in the bloodstream.¹¹

These interactions result in a dramatic increase in the epidermal turnover rate, accelerated mitotic rate, and an increased absolute number of the germinative skin cells. The

time required for cells to mature and travel through the epidermis is decreased and is manifested as an increased loss of epidermal material, together with a significant loss of protein and folate.^{14,28,30,36} Scales are composed of materials that are retained by the skin, such as soluble proteins, amino acids, and nucleic acids. In such patients, the daily loss of scales increases from 500–1000 mg to 20–30 g.²⁸

Immunohistochemical studies are performed to distinguish between benign and malignant erythroderma causes. The immunophenotypic characteristics of benign (psoriasis, dermatitis, drug induced) and malignant (Sézary syndrome, mycosis fungoides) forms of erythroderma, are similar.²⁹ In immunohistochemical studies,²⁷ the dermal infiltrate in patients with Sézary syndrome mainly showed a T-helper-2 cytokine profile, whereas benign reactive erythroderma showed a T-helper-1 cytokine profile, indicating that, although clinically similar, they have different underlying pathogenic mechanisms. In addition to these basic alterations, all earlier mentioned disorders have their own specific pathogenesis. A recently performed study on the expression of the programmed death-1 protein (PD-1, or CD279), which is expressed by activated T cells, examined 30 patients exhibiting different types of erythrodermic inflammatory diseases (EIDs) (2 paraneoplastic, 6 psoriatic, 10 atopic, and 12 idiopathic), and 25 patients with Sézary syndrome by obtaining skin biopsies and applying a panel of T-cell markers. The study determined that 92% (23 out of 25) of the Sézary syndrome cases exhibited PD-1 expression by more than 50% of infiltrating T cells; in contrast, PD-1 expression by more than 50% of infiltrating T cells was observed in only 13% (4 out of 30) of the EID cases. Sézary syndrome is associated with PD-1 expression by CD4+ neoplastic T cells, while EIDs are mainly associated with PD-1 expression by CD8+ T cells. In this context, PD-1 expression by more than 50% of CD4+ T cells along with the expression of CD7 by 20% or more of infiltrating T cells in skin biopsies is supportive of a Sézary syndrome diagnosis in erythroderma patients.²⁵

CLINICAL PRESENTATION/CONNOTATION

The Skin: Erythroderma can either develop acutely within the frame of a few hours or appear more gradually over the course of several days, weeks, or months after initially showing patches of pruritic erythema.¹⁴

The patch(es) enlarge and coalesce to form extensive areas of erythema, which eventually spread to cover all or most of the skin surface. Erythematous patches may generally reflect the characteristics of the underlying condition initially, the specific features of the underlying diseases are often lost after erythroderma has fully developed.¹⁴ Depending on the extent to which the erythroderma has progressed and the underlying diseases, the scaling associated with erythroderma will vary significantly in both color and size.³⁶

The acute form is heralded by the formation of large scales, whereas the chronic form is recognized by small scales. The skin is conspicuously bright red, dry, scaly, hot, and indurated. Mild to severe pruritus is usually present. Scratching and rubbing may lead to secondary lichenification and linear crusted erosions. Patients with PRP and Sézary syndrome may also exhibit hyperkeratosis on their palms and soles (palmo-plantar keratoderma).¹⁴ Drug-induced erythroderma may also cause facial edema.³⁰

The sudden eruption of seborrheic keratosis, known as the sign of Leser-Trélat, has been observed in cases with

erythroderma, secondary to inflammatory dermatoses (such as psoriasis, dermatitis, and PRP, or those caused by malignancies and drug reactions). Resolving erythrodermic dermatitis also has the effect of diminishing the skin lesions; for example, transient seborrheic keratoses.^{37,38}

Eye: Periorbital skin inflammation and edema may cause ectropion and epiphora. Involvement of the eyelids may show blepharitis, epiphora (excessive tearing), and ectropion (eyelid eversion).¹⁴

Nail: The nails become thick, lusterless, dry, brittle, and show ridging of the nail plate.⁴ Other accompanying symptoms include nail dystrophy, nail shedding (onychomadesis), splinter hemorrhages, paronychia, and Beau lines. Drug-induced erythrodermas, in particular, can be associated with shore-line nails, exhibiting alternating bands of discontinuity in the nail plate.^{30,39}

Hair: Chronic erythroderma patients may exhibit scaling in the scalp, telogen effluvium,¹⁴ and diffuse nonscarring alopecia.^{14,36}

Systemic Findings: Constitutional symptoms can be seen including malaise, fatigue, fever, or hypothermia.¹⁴ Lymphadenopathy, hepatosplenomegaly, edema of the feet/ankles, and gynecomastia may also be observed. The basal metabolic rate is increased, and a catabolic state causes significant weight loss over time. At times, patients can slip into an irreversible hypothermia or hyperthermia. The former may result in ventricular bradycardia and hypotension. An increased peripheral blood flow may result in high-output cardiac failure. Protein and fluid loss is the cardinal feature that can lead to severe illness. Edema, swelling from fluid retention, especially around the ankles, may develop, along with infection. The body may not be able to maintain its temperature, producing shivering episodes. Pneumonia and congestive heart failure may occur and often require hospitalization. Its precise etiology is debatable. All body systems may be affected by these manifestations. The general picture is modified according to the nature of the underlying disorder.^{1,19}

Cutaneous Disorder

Psoriasis

Psoriasis is the most common underlying disorder (see Figure 21.1 for psoriatic nail), and its features may be present until the whole body develops exfoliative dermatitis. Patients might also have a history of prior plaque development, systemic steroid use, withdrawal of potent topical or oral corticosteroids, psoralen plus UVA (PUVA) therapy, cyclosporine or methotrexate use, tar treatment, biologic drug phototoxicity, intermittent infections, severe sunburn, hypocalcemia, allergic drug-induced eruption that results in the Koebner phenomenon, emotional stress, alcoholism, or pregnancy.^{1,19,36} (Figures 21.2 through 21.4).

Erythrodermic psoriasis is characterized by lesions that are not clearly defined, lesions that are widespread, and fiery-red exfoliation/shedding of the skin. Exfoliation often occurs in large sheets instead of smaller scales, often associated with severe itching and pain. After the erythema becomes generalized, the usual characteristics of the psoriatic plaques will gradually disappear, and disseminated sterile subcorneal pustules will develop instead. The loss of proteins and fluids is the main feature of the condition that results in detrimental effects for the patients. Swelling and edema caused by fluid retention might develop, especially around the ankles; swelling may also



Figure 21.1 Erythrodermic psoriatic nail.



Figure 21.2 Psoriatic erythroderma.

be accompanied by infection. The body might lose its ability to regulate temperature, which, in turn, might trigger episodes of shivering in patients. Hospitalization is generally required for severe erythrodermic psoriasis. Its exact etiology has not yet been elucidated. The nail changes, including nail pits, oil drop, and onycholysis, may help to make the diagnosis.³⁶ Sudden withdrawal of systemic treatment, the appearance of psoriasis at the site of skin injuries, allergic drug-induced dermatitis, leading to the Koebner phenomenon, systemic steroid use, infections, severe sunburn, alcoholism, and emotional stress may also trigger the condition.



Figure 21.3 Childhood psoriatic erythroderma.



Figure 21.4 Erythroderma/exfoliative dermatitis.

Generalized pustular psoriasis (von Zumbusch) is a rarely observed and more severe type of psoriasis. Patients with this condition also exhibit frequent episodes of fever, hypocalcemia, cachexia, and erythroderma. A number of cases of acute respiratory distress syndrome associated with pustular and erythrodermic psoriasis have been reported. Other systemic complications include pneumonia, congestive heart failure, and hepatitis.³¹

Congenital erythrodermic psoriasis is extremely uncommon, which is also true in infancy; however, its incidence is directly proportional to the increase in age. The clinical features of psoriasis are similar to those observed in adults with psoriatic erythroderma (Figure 21.5).^{1,32} The prognosis of the condition is poor in infants and young children.^{7,33}

Atopic Dermatitis

This condition is a well-conceived clinical cutaneous expression of atopy. It is a pruritic, eczematous dermatosis, the clinical manifestations of which chronically fluctuate with remissions and relapses (Figure 21.6).



Figure 21.5 Erythroderma/exfoliative dermatitis.

Most individuals with atopic dermatitis have an atopic diathesis identified through personal or family history of asthma, allergic rhinitis, and/or conjunctivitis and atopic dermatitis and/or predisposition to overproduction of immunoglobulin E (IgE) antibodies. Infants and children are most commonly affected. Erythema, exudation, papules, vesiculopapules, scales, and crust are its salient acute lesions. It may transform itself into erythroderma.^{1,19,40,41} The pruritus is intense, and secondary excoriations or prurigo-like lesions are frequently observed.³⁶ Despite being widespread, the child is apparently well and thriving. Sparing of axilla and groins distinguishes it clinically from seborrheic dermatitis in typical cases.^{1,19,40,41}

It is clinically difficult to differentiate erythrodermic cutaneous T-cell lymphoma from atopic dermatitis. Clinical and laboratory characteristics, such as serum levels of lactate dehydrogenase, soluble interleukin-2 receptors, immunoglobulin E (IgE), and several chemokines, are not significantly different between erythrodermic cutaneous T-cell lymphoma and atopic dermatitis. Histologic findings, negative RAST reactions,



Figure 21.7 Erythrodermic pityriasis rubra pilaris.

Sézary cells in the peripheral blood, low serum allergen-specific IgE levels, and CCR10 positivity along with high CD4/CD8 ratios in skin lesions may aid clinicians in distinguishing erythrodermic cutaneous T-cell lymphoma from atopic dermatitis.⁴²

Pityriasis Rubra Pilaris

Erythroderma, following PRP, is fairly diagnostic, as it usually starts in childhood or adulthood^{43,44} and the lesions occupy the hair follicle in the form of papules and/or plaques with "islands of sparing." Reddish follicular papules and/or plaques with thick, dry scales comprise its cardinal clinical expression (Figures 21.7 and 21.8). Hyperkeratosis of the palms and soles, generally accompanied by fissures, is also observed. Hyperkeratosis often extends upward from the sides of the sole,



Figure 21.6 Erythrodermic atopic dermatitis.



Figure 21.8 Erythrodermic pityriasis rubra pilaris.



Figure 21.9 Pityriasis rubra pilaris, sandal sign of the plantar region.

forming a patch that overall appears like a “sandal” (Figures 21.9 and 21.10) Invariably, it has an acute onset and is usually accompanied by pruritus. It is inherited as an autosomal dominant trait with variable expression and reduced penetrance. The familial form of PRP typically begins in early childhood with a gradual onset, and most of the familial cases are of type V (atypical juvenile type). The remainder of the familial cases belong to either type III (classic juvenile) or type IV (circumscribed juvenile).^{43–47}

Seborrheic Dermatitis

This condition is a fairly common cause of erythroderma in children, less so in adults, and presents as erythematous moist, scaly lesions that occupy the seborrheic sites, namely scalp, axilla, neck, napkin, retroauricular area, and front and back of the chest. The scales are large, greasy, and yellow.^{10,31} The generalization and progression of the lesions may result in erythroderma, particularly in infants. Immunosuppression might also



Figure 21.10 Pityriasis rubra pilaris, sandal sign of the plantar region.

be observed in a small portion of these infants. Among adults, the generalization of the eruptions can trigger psoriatic erythroderma or mycosis fungoides.³¹ It may be difficult to distinguish erythrodermic seborrheic dermatitis from atopic dermatitis or psoriasis. The fact that seborrheic dermatitis improves spontaneously over the course of several weeks or months might help in distinguishing this condition from psoriasis or atopic dermatitis, because the latter tend to be prolonged and chronic conditions.³⁴

Ichthyosis

Several syndromes with ichthyosis as an important component may be responsible for erythroderma in infants and children. Harlequin fetus, bullous ichthyosis, lamellar ichthyosis, and congenital ichthyosiform erythroderma (CIE) are its other clinical variants and are required to be taken cognizance of. A collodion membrane encasement is an essential part of both CIE and lamellar ichthyosis. In CIE, it is replaced with exfoliative erythroderma, whereas in lamellar ichthyosis it is followed by generalized ichthyosis with plate-like scales. Infants with harlequin ichthyosis are born with generalized thick hyperkeratotic covering, which may prove fatal following acute respiratory distress.

Bullous ichthyosis (epidermolytic hyperkeratosis) may initially appear as generalized erythema, blistering, and scaling that develop soon after birth or during childhood. Gradually, blistering diminishes and is replaced with ichthyosiform erythroderma with overt clinical features. The larger joint areas of the body might become covered with prominent hyperkeratotic plaques. The clinical picture and course, as well as the cutaneous signs and symptoms of epidermolytic hyperkeratosis vary considerably and may be characterized by hyperkeratosis, blistering, erythroderma, and palm and sole involvement.^{7,48–50}

Diffuse Cutaneous Mastocytosis

This condition is a rare entity in which the entire skin is heavily infiltrated with mast cells.⁵¹ In newborns, diffuse cutaneous mastocytosis should be suspected in the presence of clinical findings indicating diffuse erythema along with episodes of blistering and vesiculation.³⁴

Trivial injury, trauma, and pressure may cause extensive urtication and bullae formation. Symptoms include blistering, itching, hypotension, abdominal pain, gastrointestinal bleeding, diarrhea, flushing, and vomiting. Due to the detrimental effects on the circulatory system and the possibility of anaphylactic shock caused by the sudden degranulation of mast cells, the progression of this condition can be very severe or even potentially fatal.³⁴ Unlike the adult-onset variety, cutaneous mastocytosis of infancy and childhood may regress spontaneously.⁵¹

Bullous Dermatoses

Bullous dermatoses are a rare cause of erythroderma. Among these different bullous diseases, pemphigus foliaceus is the one most often reported to cause erythroderma; bullous pemphigoid and paraneoplastic pemphigus, on the other hand, are rarely implicated in erythroderma. In pemphigus foliaceus, superficial erosions and flaccid impetigo-like blisters are followed by scale-like crusts and collarettes of scale.³⁶ With bullous pemphigoid, tense blisters are observed in early lesions; urticarial plaques, superficial ulcers, and deep erosions may also appear, often accompanied by generalized pruritus.³⁰



Figure 21.11 Erythrodermic mycosis fungoides.

Malignancies

Erythroderma may precede, accompany, or follow cutaneous T-cell lymphoma (CTCL), and its appearance may be identical to that of benign erythroderma. An immunophenotypic study with the use of advanced antibody panels may be required to distinguish it from the benign form.⁵² CTCL is a rare entity in children and is likely to be overlooked; however, in particular cases its features are lymphadenopathy, splenomegaly, and lymphocytosis.

CTCL-related erythroderma is divided into erythrodermic mycosis fungoides and Sézary syndrome (SS) (Figures 21.11 and 21.12). In mycosis fungoides patients, lesions on the skin merge and eventually develop into an erythroderma without the involvement of the blood; such erythroderma is referred

to as erythrodermic mycosis fungoides.^{42,53} The revised ISCL/EORTC staging described three types of blood involvement in CTCL: B0, where circulating Sézary cells (CSC) are less than 5%; B1, where CSC is greater than 5%, and less than 1000/mm³; and B2, where CSC is greater than 1000/mm³.⁵⁴ Of these three types, B0 and B1 are indicative of erythrodermic mycosis fungoides, while B2 is indicative of Sézary syndrome.⁵⁴

Sézary syndrome refers to the concurrent presence of the following three clinical features: generalized lymphadenopathy, circulating malignant T lymphocytes, and erythroderma. Sézary syndrome may also be accompanied by diffuse alopecia, keratoderma, and leonine facies. The skin of Sézary syndrome patients can be hyperpigmented (melanoerythroderma) and highly infiltrated. Extensive pruritus is also commonly observed. Other findings include electrolyte imbalances, hypothermia, eyelid changes/ectropion, and hair loss. The syndrome can be overlooked in the elderly, because clinicians might associate the pruritus and dry skin in older patients with advancing age.^{36,52} The diagnosis of Sézary syndrome is based on the presence of T-cell clones in the blood, erythroderma, and one of the following factors: (1) a CD4 : CD8 ratio of $\geq 10:1$; (2) a higher percentage of CD4+ cells with abnormal phenotypes ($\geq 40\%$ CD4+/CD7- or $\geq 30\%$ CD4+/CD26-); or (3) ≥ 1000 Sézary cells/mm³.⁵⁴ Individuals with Sézary syndrome usually show rapid disease progression compared to mycosis fungoides. Although Sézary syndrome and mycosis fungoides are classified as distinct, separate entities, some cases of mycosis fungoides can evolve into Sézary syndrome.⁵³

Cutaneous T-cell lymphoma (CTCL) is a rarely encountered and often overlooked condition in children characterized by splenomegaly, lymphocytosis, and lymphadenopathy.

Other malignancy-related causes include malignancies in the internal blood vessels. These are generally observed in elderly individuals; in such patients, erythroderma serves as an indicator of the internal malignancy.^{4,13,14,26-29} Such malignancies may lead to the development of erythrodermas, including acute and chronic leukemia, malignant histiocytosis, and reticular cell sarcoma. Carcinomas of the larynx, esophagus, lungs, prostate, colon, thyroid, and fallopian tubes might also be implicated in the development of erythroderma. In patients where erythroderma progression is more debilitating, insidious, and resistant to treatment, and where there is no previous history of skin disorders, physicians should consider the possibility of malignancy-induced erythrodermas.^{1,15,37-39}



Figure 21.12 Erythrodermic mycosis fungoides.

DRUG REACTIONS

Topical and systemic medications are notorious for precipitating erythroderma/exfoliative dermatitis. An apparent increase in the drug-induced instances may be directly proportional to the introduction of new drugs.^{1,14,24,34-36} The inventory of drugs causing erythroderma/exfoliative dermatitis is increasing; however, the most common are shown in Table 21.3.

Erythroderma induced by drugs is two times more common among men than women. It is particularly more prevalent among the elderly.⁵⁵ In contrast to other causes of erythroderma, drug-induced erythroderma is characterized by rapid onset, progression, and resolution.⁵⁶ Many drug eruptions that commonly present as morbilliform, lichenoid, or urticarial forms may often progress to extensive erythema and exfoliation. This rapidity may serve as an indication that a drug is the causative agent of the erythroderma (Figure 21.13). Leukonychia may also be observed in patients exhibiting drug-induced erythroderma.¹⁶

Table 21.3 Common Drugs Causing Exfoliative Dermatitis in Adults

Acetaminophen	Minocycline
Actinomycin-D	Nitrofurantoin
Allopurinol	Nifedipine
Arsenic	Omeprazole
Barbiturates	Para-amino salicylic acid
Beta blockers	Paracetamol
Calcium channel blockers	Plaquenil
Captopril	Penicillin
Carbamazepine	Phenobarbital
Cefoxitin	Phenothiazine
Chloroquine diphosphate	Phenytoin
Chlorpromazine	Quinidine
Cimetidine	Ranitidine
Dapsone	Rifampicin
Gentamycin	Streptomycin
Gold	Sulfadiazine
Griseofulvin	Sulfonylurea
Hydantoin sodium	Tetracycline
Interferon	Thalidomide
Isoniazid/isonicotinic hydrazide	Tobramycin
Isotretinoin	Tolbutamide
Ketoconazole	Trimetoprim-sulfamethoxazole
Lithium	Vancomycin
Mercurials	

Source: Data adapted from Sehgal VN, Srivastava G, Sardana K. *Int J Dermatol* 2004;43:39–47. With kind permission from Springer Science+Business Media: *Cutaneous Drug Eruptions*, London: Springer, Drug eruptions and erythroderma. 2015, 251–258, Jadotte YT et al., In: Hall JC, Hall BJ, editors.

**Figure 21.13** Drug hypersensitivity syndrome.

Drugs commonly incriminated are sulfonamides, penicillin, isoniazid, antimalarials, allopurinol, phenytoin, omeprazole, captopril, and vancomycin.^{16,55} Apart from the well-known allopathic medicines, homeopathic, Unani, Ayurvedic, herbal, and common home remedies have been incriminated.^{1,19}

Some patients may develop erythroderma as a result of a “drug rash with eosinophilia and systemic symptoms” (or DRESS) syndrome—also called drug-induced hypersensitivity syndrome (DIHS).¹⁶ In addition to erythroderma, DRESS syndrome can be associated with severe and life-threatening involvement of the viscera accompanied by fever, hepatitis, lymphadenopathy, rash, and leukocytosis. Skin lesions are generally patchy erythematous macules and erythematous papules

that can be confluent and pruritic; in some cases, the lesions can also be hemorrhagic, targetoid, and erythrodermic.^{16,57} In patients with erythroderma, attention should be paid to possible involvement of the viscera, because the erythroderma might prove to be one of the signs of the DRESS syndrome.¹⁶

Drug-induced erythroderma due to dapsone/antileprosy drug hypersensitivity may often mimic cutaneous T-cell lymphoma in terms of both clinical features and histopathology. Fortunately, it resolves after withdrawal of the offending drug(s) and the administration of supportive therapy. Additionally, many drugs may lead to pseudo-Sézary syndrome including enalapril, amiloride, fosinopril, hydrochlorothiazide, carbamazepine, phenobarbital, and phenytoin. In addition, flow cytometry showed a population of “Sézary-like” CD4+ T cells in the peripheral blood. Skin biopsies revealed numerous atypical and epidermotropic lymphocytes, and the predominant T-cell clonality was similar between the peripheral blood and skin. The eruption fully resolved following cessation of the antihypertensive drugs.⁵⁸

Drug-induced erythroderma in children is commonly observed with sulfonamide, isoniazid, streptomycin, non-steroidal antiinflammatory drugs, and antiepileptic drugs; however, cases have also been recorded with Ayurvedic, Unani, homeopathic, and indigenous medications (Table 21.3).

A history of drugs for certain dermatoses/systemic disorders may be elicited prior to the onset of exfoliative dermatitis. Erythema is acute in onset and progresses to generalized exfoliation, which may resolve over the course of 2–6 weeks.¹ Topical preparations have caused generalization of the existing dermatoses in a proportion of cases. If the incriminating drug(s) is withdrawn and symptomatic treatment instituted, the prognosis is excellent.⁵⁹

Toxic Epidermal Necrolysis (TEN)

This involves widespread blistering of the skin and/or mucous membranes. TEN can be suspected in patients with rapidly progressing and widespread desquamation accompanied by hypotension, fever, and organ involvement. Symptoms and signs of TEN include erythroderma, lesions with dusky centers, and considerable pain despite the absence of any visible skin abnormalities.^{59–62}

There is an extensive sloughing of the epidermis and dermis, and underneath the slough is “naked” and is attended by enormous exudation. There also may be considerable loss of proteins and electrolytes. There is impaired thermoregulation and altered immunologic function; hence, patients are infection prone. This reaction pattern is mediated through the breakdown products or toxins of the microorganism, antibiotic medication administered to treat infective disorders, and/or polysorbate toxicity. Medications, including allopurinol, antimicrobials, and antiepileptic drugs, are frequent culprits.^{60–61} The condition is most frequently encountered in adults but occasionally has been reported in infants.^{59–62}

Infections

Staphylococcal Scalded Skin Syndrome (SSSS)

Unlike other erythrodermas in children, SSSS onset is acute and accompanied by fever, systemic toxicity, and a positive Nikolsky sign. The erythema is generalized rapidly and progresses to sloughing and erosions; diffuse erythema with superficial desquamation and/or bullae not involving the mucous membranes suggests SSSS.¹⁴ Histopathologic examination often will

distinguish it from toxic epidermal necrolysis. Occasionally, widespread staphylococcal pustulation resembling generalized candidosis may develop in a healthy child; however, nasopharynx, axillary skin, urine, and blood culture are usually positive for *Staphylococcus*; however, cultures obtained from unruptured bullae will be negative. SSSS is a potentially fatal disorder generally associated with rapid progression.^{10,14,34,60}

Toxic Shock Syndrome

The clinical features of this condition include fever, hypertension, and diffuse macular blanching erythroderma, followed by desquamation of the palms and soles. Dysfunction of various organs or systems may be life threatening. Surgical wound infection of the skin, subcutaneous and/or soft tissue, and also of bone may be predisposing factor(s).^{10,59}

Scarlet Fever

This condition forms an important differential diagnosis of rubella, toxic shock syndrome, severe staphylococcal infection, drug eruptions, mononucleosis, and exanthem subitum. The erythroderma is transient and successfully resolves following administration of penicillin/erythromycin.^{10,59}

Syphilis

In the first 6 to 8 weeks following birth, early congenital syphilis can be associated with superficial scaling and widespread erythema.³⁴ Clinicians should suspect syphilis, if widespread desquamation, as well as sole and palm involvement accompanied by bullae, are present. The clinical presentation of syphilis in infants also includes fever, generalized lymphadenopathy, hepatomegaly, and splenomegaly. These infants may also exhibit condylomata lata.⁶³

Congenital Neonatal Candidosis

Congenital cutaneous candidosis, which is identified either at birth or in the first few days that follow, involves lesions that initially appear as maculopapular eruptions. Candidal chorioamnionitis is commonly encountered among pregnant women who have had cerclage or placement of an intrauterine foreign body (intrauterine pessary), and in the immediate postpartum period the condition may be mistaken for congenital cutaneous candidosis.⁶⁴ The disease is characterized by white maculae on the umbilical cord and placenta, along with maculopapular or sometimes bullous or pustular lesions on the newborn (a clinical colloquially referred to as "white dots on the placenta; red dots on the baby").⁶⁴

Congenital candidosis gradually supervenes with the appearance of classical pustules, especially over the palms and soles. It spreads rapidly and often involves the umbilicus and exanthem and rapidly evolves into erythroderma.⁶⁴ In contrast to neonatal candidosis that is acquired by the newborn during vaginal delivery, the diaper area and oral cavity are usually unaffected in congenital neonatal candidosis.⁶⁵ In infants born at normal term, the disease generally resolves by itself, and the infants do not suffer from any other diseases or complications.^{64,66} In prematurely born infants, on the other hand, congenital cutaneous candidosis is associated with an increased risk of candidemia and multiple organ infection.^{14,66}

The diagnosis is easy—either through the demonstration of mycelia/conidia in 10% potassium hydroxide mount or on Gram stain followed by positive culture of *Candida* spp. Sometimes systemic antifungals cause rapid resolution of the

disease, and in the neonatal form of generalized cutaneous candidosis the lesions start in the oral cavity or napkins area.^{10,67}

Crusted Scabies

Crusted or hyperkeratotic scabies is usually nonpruritic owing to impairment of the sensory nerves. It is characterized by sand-like, thick, tan crusts that flake off revealing underlining normal skin. The lesions are usually generalized. Fissures may be a constant source of fatal septic events. Crusted lesions are frequently encountered in immunocompromised HIV/AIDS and are a potential source of perpetuating the disease in the form of epidemics. The diagnosis is confirmed through the demonstration of *Sarcoptes scabiei*. A first- and second-generation screening test (enzyme-linked immunosorbent assay) followed by confirmation by Western blot is mandatory to establish the diagnosis of HIV. The condition is amenable to specific topical and oral treatment.^{68,69}

Immunologic Disorders

Omenn Syndrome/Familial Reticuloendotheliosis

This condition has infrequently been diagnosed in the recent past. The demonstration of abnormal histiocytic-appearing cells in the skin, lymph nodes, spleen, and liver is significant. Erythroderma, failure to thrive, pronounced lymphadenopathy, diffuse alopecia, hepatosplenomegaly, and recurrent severe infections are the salient clinical features. Marked leukocytosis, eosinophilia, anemia, hypogammaglobulinemia, and depressed T-cell immunity are its other findings.^{10,70–72} T lymphocytes CD4 5RO+ may be demonstrated at the molecular level,³³ and a skin biopsy may confirm the diagnosis^{33,73} and help in differentiating it from Netherton syndrome and GVHD, although it is mostly fatal. Cyclosporine and bone-marrow transplantation can be effective therapies.^{10,70–72}

Hypogammaglobulinemia

An infant who is apparently normal at birth but who subsequently develops fever, diarrhea, and rapidly progressive generalized exfoliative dermatitis (erythroderma) may have hypogammaglobulinemia. Monthly replenishment by intravenous infusion of gamma globulin alleviates fever and erythema.⁷⁴ Infants appear normal at birth but soon develop rapidly progressive generalized erythroderma accompanied by diarrhea and fever. Monthly intravenous infusions to replenish gamma globulin levels may help alleviate the erythema and fever symptoms.⁵⁷

DiGeorge Syndrome

This is a disorder characterized by progressive maculopapular/eczematous lesions that may eventually cover the entire skin surface. It is rarely the underlying cause of erythroderma. When combined with severe immunodeficiency, the child develops widespread seborrheic or eczematous dermatitis.⁵⁹

Maternal-Fetal Graft versus Host Disease

This condition occurs in infants who, unknowingly, are transfused with nonirradiated blood or have received small amount of maternal blood by placenta in utero. Usually, these infants have severe combined immunodeficiency. Its clinical presentation is a nonspecific morbilliform eruption, which gradually progresses to erythroderma with epidermal sloughing.^{10,12,58,75} It looks identical to the clinical picture of Omenn syndrome, including the cutaneous findings of erythroderma and alopecia.⁷²

Leiner Disease

This condition is composed of a group of disorders with similar presentations characterized by erythroderma, diarrhea, and failure to thrive. Some of the affected individuals with Leiner phenotype may have an associated immunodeficiency.⁷⁴ The infant is apparently normal at birth, but dermatitis and diarrhea make an early appearance, and then the latter is severe and chronic. The dermatitis is associated with progressive erythema and erosions, which may ultimately become generalized. Some patients show greater susceptibility to infections due to a yeast opsonization defect that is caused by a dysfunction in the complement's fifth component.⁷⁶ The condition does not respond to topical/oral medication. Adequate nutritional support along with hyperalimentation and individualized treatment may be helpful.^{10,74,77}

Metabolic Disorders

In rare cases, neonatal erythroderma can be caused by metabolic disorders. For example, in late infancy, severe protein deficiency (kwashiorkor) or zinc deficiency can lead to squamous erythematous lesions that initially begin in the periorificial areas. In neonates, skin lesions in conjunction with neurologic manifestations are suggestive of underlying metabolic causes. This is especially the case with disorders affecting the urea cycle and carboxylase metabolism (e.g., argininosuccinic aciduria, citrullinemia). Erythroderma and alopecia are often, but not always, observed with such disorders.^{6,66} Among different hereditary metabolic disorders, the holocarboxylase synthetase deficiency (which affects biotin metabolism) and the Sjögren-Larsson syndrome appear to be relatively more frequent causes of erythroderma in infants.⁶⁴

Sjögren-Larsson Syndrome (SLS) is an autosomal recessive metabolic disease that arises from the mutation of the *ALDH3A2* gene that encodes the enzyme fatty aldehyde dehydrogenase. It is associated with severe neurocutaneous symptoms.⁶⁴ In addition to the development of erythroderma during infancy, the syndrome includes the following symptoms: ichthyosiform erythroderma, psychomotor retardation, and spastic diplegia.⁶⁴ The diagnosis is made on the basis of enzyme assays on leukocytes and fibroblasts, along with a skin biopsy, which may reveal a deficiency of enzyme fatty alcohol oxidoreductase.⁶⁶

Holocarboxylase synthetase deficiency is an extremely rare autosomal recessive metabolic disease, caused by a defect that alters the incorporation of biotin (vitamin B7) into biotin-dependent enzymes such as pyruvate carboxylase and acetyl-CoA carboxylase. It is characterized by severe neurologic manifestations and life-threatening ketoacidosis. In infants, this disorder may also lead to alopecia, along with erythroderma that involves the periorificial areas.⁶⁴

Kwashiorkor

This is a common form of routine malnutrition in both underdeveloped and developing countries. It may present with generalized erythema, edema, and increased skin fragility. Excessive protein loss may result in renal and/or hepatic failure in older children.¹⁰

Acrodermatitis Enteropathica

This condition is a well-recognized clinical entity in infants and children. AE is associated with periorificial and acral dermatitis, alopecia, and/or diarrhea, but all three of these signs are concurrently observed in only 20% of patients. In AE,

cutaneous lesions are generally the first sign. AE presents with scaly, crusted, erythematous, psoriasiform, vesiculobullous, or eczematous eruptions all across the body, including the orifices, the extensor surfaces of major joints, the scalp, and the acral sites.⁷⁸ In addition to low serum zinc levels, serum alkaline phosphatase levels are also reduced, as this enzyme is zinc dependent. A similar condition may be observed in children with AIDS.^{10,79}

Cystic Fibrosis

Initial presentation of this disease is quite different and is characterized by the development of severe, rapidly progressive, and unresponsive psoriasiform lesions.⁸⁰ The associated dermatitis appears as a psoriasiform diaper dermatitis that does not respond to topical steroid or antifungal treatment. Cystic fibrosis dermatitis can spread over the body and leads to irritability and growth retardation.⁸¹ Pulmonary and gastrointestinal components complicate the condition later. The skin lesions may resolve following administration of pancreatic enzymes and nutritional supplements.⁸⁰

Amino-Acid Disorders

Several reports have demonstrated the deficiency of various amino acids and their association with erythroderma.

Acrodermatitis enteropathica-like erythroderma occurs in infants affected by maple syrup urine disease and those who are on a low isoleucine diet. Secondary candidal infections are not uncommon in these patients. Such dermatitis was similarly reported for arginine deficiency, citrullinemia in newborns, and carbamoyl phosphate synthetase deficiency.^{6,81,82}

VARIOUS SYNDROMES

Trichothiodystrophy (Tay Syndrome)

The affected newborn may have collodion membrane and erythroderma with other features, including brittle, sparse hair, variable ichthyosis, and central nervous system manifestations. Erythroderma resolves itself during infancy.^{10,83}

Netherton Syndrome

Infants and children affected with this disorder show a generalized exfoliative erythroderma. Trichorrhexis invaginata (bamboo hair) and atopy are its other features. The disease may be confused with generalized atopic dermatitis.⁸⁴ Erythroderma evolves in childhood into a distinct eruption with serpiginous borders, "ichthyosis linearis circumflexa," which is the classic rash of the Comèl-Netherton syndrome.⁷²

A genetic linkage has been established to the *SPINK-5* gene locus on chromosome 5q32 encoding the serum protease inhibitor LEKTI. This information may be useful in prenatal testing in any subsequent pregnancy of the mother of the affected child.⁸⁴

Keratitis-Ichthyosis-Deafness

Keratitis-ichthyosis-deafness syndrome is a rare disorder in which the infant usually has diffusely thickened erythematous skin that peels off in the course of the first week of life. Subsequently, atypical prominent follicular keratosis is identified over the head and extremities. In the following years or decades, keratoconjunctivitis with noticeable vascularization (pannus), along with neurosensory deafness, occurs.⁸⁵

Neutral Lipid Storage Disease with Ichthyosis (Dorfman-Chanarin Syndrome)

This condition resembles CIE. Demonstration of lipid vacuoles in the skin and elsewhere in the body supports its diagnosis. It may also have features such as cataract, myopathy, sensory-neural deafness, and growth retardation.^{10,86}

Conradi-Hünemann Syndrome

This condition affects infants and is characterized by the presence of bands of ichthyosiform erythroderma and hypopigmentation along the lines of Blaschko. The bands resolve in due course, leaving behind follicular atrophoderma. Extracutaneous signs include dwarfism, cataracts, and psychomotor retardation. Radiography shows an asymptomatic, focal, enchondral calcific strippling.^{10,14,87}

HEMODYNAMIC/METABOLIC DISTURBANCES

The disease may cause an enormous aberration of body metabolism. The increased skin blood flow may cause hypothermia and profound heat loss. Compensatory hypermetabolism and an increased basal metabolic rate without any primary increase in thyroid activity may ensue. Excessive protein loss through scaling and leaking through skin, hemodilution due to the increased plasma column, and hypermetabolism may contribute to hyperalbuminemia and severe edema. High-output cardiac failure may occur at any time.^{1,2,14,30,36}

HISTOPATHOLOGY

The histopathology of erythroderma/exfoliative dermatitis often reveals a nonspecific picture, consisting of orthokeratosis

(hyperkeratosis, parakeratosis), acanthosis, and a chronic perivascular inflammatory infiltrate with or without eosinophilia. The clinicopathologic correlation in erythroderma is difficult, because the specific features of the dermatosis are masked by the nonspecific features of erythroderma. In a study on Sézary syndrome, the diagnosis was established by the clonal population of T cells in the blood, despite a lack of diagnostic features on biopsy.⁸⁸ Other clinicians advocated that the submission of multiple simultaneous biopsies from the affected skin enhanced the accuracy of the histopathologic diagnosis, and the cause could be identified in up to one-half of cases.⁸⁹ The stage of the disease can modify the histopathologic picture; in the acute stage, spongiosis and parakeratosis are prominent, whereas in the chronic stage acanthosis and elongated rete ridges are seen. Despite the uniformity of the clinical expression of erythroderma, diagnostic histopathologic features of the underlying disease are retained in the majority of patients.⁹⁰ Skin biopsies from characteristic clinical lesions may often confirm the diagnosis of psoriasis, PRP, ichthyosiform erythroderma, or pemphigus foliaceus.^{1,90} Microscopic clues to the diagnosis of erythroderma, if reviewed systematically, can reveal the underlying diagnosis (Table 21.4).

The study confirms that while psoriasis and atopic dermatitis are chronic and associated with distinct histologic characteristics (e.g., perivascular eosinophils and vesiculation suggest atopic dermatitis, while acanthosis, hypogranulosis and epidermal neutrophilic microabscesses suggest psoriasis), there are no specific histologic findings that can confidently distinguish these diseases from erythroderma. Interestingly, it has been observed that eosinophils are present in lesions associated with chronic psoriasis and atopic dermatitis, with their frequency increasing during disease exacerbations. Although the presence of eosinophils in inflammatory infiltrate

Table 21.4 Histological Clues to the Diagnosis of Erythroderma

Disease	Histologic clues
Psoriasis	Parakeratosis, Munro microabscess, suprapapillary plate thinning, squirting papillae, regular acanthosis
Cutaneous T-cell lymphoma (CTCL)/Sézary	Exocytosis of mononuclear cells, epidermotropism, Pautrier microabscesses
Drug reaction	Vascular change, necrotic keratinocytes
Actinic reticuloid	Hyperkeratosis, acanthosis, superficial and deep mixed dermal infiltrate with some atypical mononuclear cells
Pityriasis rubra pilaris (PRP)	Alternating orthokeratosis and parakeratosis (vertically and horizontally) with or without keratotic plugging
Sarcoidosis	Dermal noncasketing epithelioid "naked" cell granulomas; occasional, giant cells surrounded by sparse lymphocytes
Contact dermatitis	Spongiosis, eosinophils within dermal infiltrate
Lymphoproliferative diseases	Interstitial pattern of atypical cells between collagen bundles
Scabies	Perivascular and interstitial infiltrates with eosinophils, scabetic mite/scybala/fecal pellets in stratum corneum
Dermatophytosis	Focal parakeratosis, hyphae in stratum corneum
Pemphigus	Suprabasal intraepidermal cleavage, acantholytic keratinocytes, (acantholytic cells), direct immunofluorescence depicting IgG-bound cell surface, circulating antibodies
Pemphigoid	Subepidermal bulla with eosinophils
Acute graft versus host disease	Vacuolar change, satellite cell necrosis
Atopic dermatitis	Spongiosis, eosinophils within dermal infiltrate
Seborrheic dermatitis	Parakeratosis with neutrophils at lips of follicular ostia
Dermatomyositis/subcutaneous lupus erythematosus	Vacuolar change, colloid bodies increased dermal mucin
Idiopathic subacute	Parakeratosis, spongiosis, epidermal hyperplasia, papillary dermal edema, superficial perivascular lymphohistiocytic infiltrate
Idiopathic chronic	Compact hyperkeratosis, psoriasiform hyperplasia, little spongiosis, papillary dermal thickening

Source: Data adapted from Sehgal VN, Srivastava G, Sardana K. *Int J Dermatol* 2004;43:39–47.

is usually characteristic of atopic dermatitis, eosinophils can also be detected in psoriasis lesions, especially if the disease is advanced/severe or erythrodermic.⁹¹ Higher levels of CD8+ lymphocytes in dermal infiltrate are indicative of actinic reticuloid (chronic actinic dermatitis).¹⁴ The performance of a direct immunofluorescence assay is necessary for patients suspected of having immunobullous disease—based on the presence of subepidermal bullae or intraepidermal bullae, or on the urticarial appearance of the erythroderma.¹⁴ Erythroderma induced by drugs can often be nonspecific and associated with perivascular lymphocytic infiltrate, parakeratosis, hyperkeratosis (in the form of extensive scaling), and acanthosis (in the form of peeling in the epidermis). Eosinophilia can also be observed together with leukocytosis.¹⁶

In erythroderma due to lymphoma, the infiltrate may gradually become polymorphic until it acquires specific diagnostic features. This makes repeated skin biopsies, additional investigations of lymphocytes in peripheral blood, and sustained follow-up in dubious situations mandatory to permit the correct diagnosis.⁸⁹ Additional tests to increase the diagnostic specificity include immunophenotyping and direct immunofluorescence.⁹¹ The histopathologic characteristics of Sézary syndrome and of erythrodermic mycosis fungoides vary considerably, and may include uncommon features such as Pautrier microabscesses, haloed lymphocytes, and epidermotropism. Studies indicate variations in the pattern of dermal lymphocytes from the superficial perivascular to dense lichenoid infiltrate, which suggests that Sézary syndrome and erythrodermic mycosis fungoides may have more subtle characteristics compared to plaque or patch mycosis fungoides.⁵² The identification and quantification of Sézary cells in order to diagnose Sézary syndrome and erythrodermic mycosis fungoides with leukemic involvement have been conventionally performed based on morphologic identification in peripheral blood smears. Atypical lymphocytes with cerebriform nuclei can also be identified in the blood of patients with benign inflammatory skin diseases, as well as in healthy persons. Flow cytometry can be used to detect neoplastic T cells, which characteristically are CD4+ CD26-. Benign inflammatory dermatoses can also be associated with CD7-CD26 T cells.^{52,92,93}

In a study performed by the Cutaneous Lymphoma Task Force (CLTF), a group affiliated with the European Organization for Research and Treatment of Cancer (EORTC), numerous skin samples were obtained from erythrodermic patients to evaluate the diagnostic features that distinguish erythrodermic inflammatory diseases and Sézary syndrome. Important histopathologic criteria for the distinction of Sézary syndrome from erythrodermic inflammatory diseases are the presence of Pautrier microabscesses and a diffuse and deep pattern of the dermal infiltrate, which were both seen exclusively in Sézary syndrome samples. Increased epidermotropism is an important and differentiating characteristic of Sézary syndrome. Blastic or atypical cerebriform lymphocytes are also observed more frequently in Sézary syndrome than they are in erythrodermic inflammatory diseases. Immunohistochemical assessments of Sézary syndrome also indicate reduced infiltration by CD8+ cells, significant decreases in CD7 expression, and levels of PD-1 and MUM-1 expression, and increased proliferation (Ki-67+). In this context, the diagnosis of the Sézary syndrome may require the immunohistochemical and histopathology examination of one or several skin biopsies; however, despite this requirement, clinicopathologic correlation remains

an important tool for establishing the diagnosis of Sézary syndrome.⁹⁴

In nearly 30% of erythroderma cases, histologic characteristics remain nonspecific during the course and progression of the disease, which renders accurate diagnosis of the underlying condition difficult.¹⁴

INVESTIGATIONS/DIAGNOSIS

Laboratory testing is based on the patient's medical history, clinical presentation, and suspected cause of erythroderma.¹⁴ Mild anemia, leukocytosis, increased erythrocyte sedimentation rate, hypoalbuminemia, hyperglobulinemia, and hyperuricemia are frequent findings.^{8,36,88} Increased IgE may be observed in erythroderma when caused by atopic dermatitis and drug reactions, although it has also been reported in other settings.⁸⁸ A decreased CD4+ T-cell count was observed in patients with erythroderma in the absence of HIV disease, as a consequence of sequestration of the lymphocytes in the skin.⁹⁵ In patients suspected of having crusted scabies, burrows should be scraped and examined for mites with the aid of a microscope. In case of suspected dermatophyte infections, potassium hydroxide (KOH) solutions can be used for detecting arthrospores and hyphae.¹⁴

Circulating Sézary cells at greater than 20% are indicative of Sézary syndrome, but at less than 10% are nonspecific findings in erythroderma. Immunophenotyping, flow cytometry, and, in particular, B-cell and T-cell gene rearrangement analysis may be helpful in confirming the diagnosis of lymphoma when it is strongly suspected.³ Actinic retinoid is differentiated from Sézary syndrome by the increased CD8+ T cells in the latter and the nuclear contour index of peripheral blood lymphocytes.⁸⁸ A detailed guide to investigations is given in Table 21.5.

A detailed history of the sequence of events leading to the development of erythroderma/exfoliative dermatitis is a prerequisite in all patients. Often the clues obtained help in diagnosis and appropriate management. A thorough clinical examination is required to diagnose the etiology of exfoliative dermatitis and to allow appropriate urgent symptomatic treatment. An astute practitioner will be able to identify the nature of the underlying dermatosis and proceed to confirm his or her suspicions. Histopathology is paramount and is rewarding in more than 50% of cases if a diligent effort is made. Fine needle aspiration cytology may be vital to distinguish between dermatopathic and malignant lymphadenopathy. Heteroduplex analysis of T-cell receptor gamma gene rearrangement can be used as an important diagnostic tool in skin biopsies to classify the underlying etiology of erythroderma.⁹⁶ T-cell clonality analysis may be useful for the diagnoses of cutaneous T-cell lymphoma in patients with erythroderma.⁹⁷ In patients in whom erythroderma is suspected to be the manifestation of occult malignancy, the radiologic workup may include chest radiograph, computed tomography, or magnetic resonance imaging (MRI) of the abdomen and pelvis, colonoscopy, mammography in women, or ultrasonography of the prostate in men.¹⁴

MANAGEMENT

All cases should be considered as dermatologic emergencies, and patients should preferably be hospitalized for treatment.

Table 21.5 Investigations/Laboratory Tests—Basic Investigations

- Weight, temperature, pulse, respiratory rate charting
- Fluid intake/output charting
- Complete hemogram, total and differential leukocyte counts, absolute platelet count, erythrocyte sedimentation rate
- Liver and kidney function tests, including serum electrolytes
- Histopathology
- Urinalysis
- Electrocardiogram (ECG) and chest radiograph

Disease-specific investigations:

- Skin scrapings/KOH (crusted scabies/extensive tinea corporis)
- Patch test (after recovery, for suspected allergic contact dermatitis, photoallergic contact dermatitis, airborne contact dermatitis)
- Serum immunoglobulin E (atopic dermatitis)
- Serum and urine protein electrophoresis (multiple myeloma)
- Angiotensin-converting enzyme levels, serum calcium (sarcoidosis)
- Cultures may show bacterial overgrowth or the herpes simplex virus
- CD4+ T-cell count/CD8+ T cells
- Human immunodeficiency virus 1 and 2 testing, including Western blot test, to exclude acquired immunodeficiency syndrome
- Immunology-antinuclear antibody, rheumatoid factor, anti-DNA
- Fine-needle aspiration cytology lymph nodes, bone-marrow examination (lymphoma/leukemia)
- Direct immunofluorescence (Pemphigus foliaceus, lichen planus, lupus erythematosus, graft versus host disease)
- Immunophenotyping, flow cytometry, and particularly, B-cell and T-cell gene rearrangement analysis—if lymphoma is strongly suspected
- Workup for occult malignancy, if suspected: chest radiograph, computed tomography scan and ECG, ultrasonography abdomen, stool for occult blood, mammography, sigmoidoscopy, prostate examination, cervical smear, as indicated

Source: Data adapted from Sehgal VN, Srivastava G, Sardana K. *Int J Dermatol* 2004;43:39–47.

Serious general medical problems may occur in due course if not appropriately treated.

The initial management of all types of erythroderma is the same regardless of the etiology. The principle of management is to maintain skin moisture, avoid scratching, avoid precipitating factors, apply topical steroids, and treat the underlying cause and complications.^{1,19,59,88} The patient requires a regulated environmental temperature, avoiding cooling and overheating. Together with general management, all unnecessary medication should be avoided. Cutaneous applications should be soothing and mild due to the already inflamed skin. Mild topical steroids/emollients after lukewarm washing can act as an antipruritic. Antihistamines (H1 receptor) can be administered to enhance the effect.

The basic management of erythroderma is supportive therapy and correction of the hematologic, biochemical, and metabolic imbalances. A regulated environmental temperature gives symptomatic relief to the affected patient. Liberal uses of emollients are useful in soothing the irritated skin. Low-potency topical corticosteroids are useful in only a few patients and may be ineffective or even harmful in other patients. The authors and other skeptics have severe reservations.^{1,59} The unfolding of underlying pathology may prove useful in defining an appropriate treatment; thus, a judicious individualized approach is required when treating erythroderma/exfoliative dermatitis in the pediatric age group.

After the acute irritated state of the skin has improved, further treatment can be undertaken according to the etiology. Antimicrobials can be added to control secondary infections. Any hemodynamic or metabolic aberrations must be addressed appropriately. Each case requires regular monitoring of protein, electrolyte balance, circulatory status, and body temperature. Blood urea, serum electrolyte, and fluid balance should be monitored.

Erythroderma commonly resists therapy until the underlying disease is treated (e.g., phototherapy, systemic medications

in psoriasis). The outcome is unpredictable in idiopathic erythroderma, and the course is marked by multiple exacerbations; prolonged glucocorticoid therapy is often needed. Appropriate inpatient/outpatient medications are influenced by the underlying etiology of erythroderma. For example, prednisone may be contraindicated in exfoliative dermatitis secondary to psoriasis, whereas retinoids are an excellent choice for this disease. Systemic steroids may be helpful in some cases but should be avoided in suspected cases of psoriasis and SSSS.⁹⁸ Agents, such as rituximab,⁹⁹ tacrolimus,¹⁰⁰ and infliximab,¹⁰¹ should be used only after weighing their potential benefits against their side effects and risks.

The treatment of patients with erythrodermic psoriasis should be treated with systemic agents, such as cyclosporine, acitretin, and methotrexate.^{14,102} In case a patient is suspected of having a drug hypersensitivity reaction, all nonessential drugs should be discontinued. Short-term administration of moderate to high doses of systemic corticosteroids (1–2 mg/kg prednisone per day) might help alleviate the hypersensitivity reaction of such patients.¹⁴

For erythrodermic atopic dermatitis patients, the administration of systemic corticosteroids or other immunosuppressants, such as methotrexate, cyclosporine, and azathioprine, might also be beneficial. For many patients, application of topical treatments might prove sufficient.¹⁴

Treatments that can be applied to pityriasis rubra pilaris patients include TNF-alpha inhibitors, methotrexate, systemic retinoids, azathioprine, and cyclosporine.^{14,103}

The ideal treatment for erythrodermic cutaneous lymphoma is still elusive. Various modalities, such as systemic steroids, PUVA, total-body electron-beam irradiation, topical nitrogen mustard, systemic chemotherapy, and extracorporeal plasmapheresis, have been tried with variable results.¹⁰⁴ A proposed plan of treatment is given in Table 21.6.¹⁰⁵

Evaluation of infants and children suffering from erythroderma/exfoliative dermatitis is paramount. It not only assists

Table 21.6 Treatment of Erythroderma

General	Specific (topical)	Specific (systemic)	Disease specific
<ul style="list-style-type: none"> • Inpatient care required • Adequate bed rest and sedation • Monitor fluid intake/electrolyte balance/temperature regulation • High protein diet/nutritional support • Discontinue all unnecessary medications 	<ul style="list-style-type: none"> • Topical steroids (triamcinolone acetonide cream 0.025%–1%) under wet dressing • Apply tap water wet dressings 2–3 times hourly; gradually reduce frequency, followed by emollients application • Daily tepid bath may be soothing. 	<ul style="list-style-type: none"> • Sedative antihistamine H1 receptor (hydroxyzine hydrochloride 25–50 mg orally every 4–6 h)/any other • Institute systemic antibiotics (to cover secondary infection by <i>Staphylococcus aureus</i>) • Systemic steroids (used with caution)—atopic dermatitis, seborrheic dermatitis; avoid in psoriasis and infections; taper down 	<p>Psoriasis—methotrexate, retinoids, phototherapy</p> <p>Atopic dermatitis—systemic steroids, antibiotics, antivirals</p> <p>Pityriasis rubra pilaris—retinoids, methotrexate, systemic steroids</p> <p>Toxic epidermal necrolysis—intravenous immunoglobulins</p> <p>Lymphoma—extracorporeal phototherapy, PUVA, alkylating agents</p> <p>Scabies—permethrin 5%, Ivermectin 200 µg/kg</p>

Source: Data adapted from Sehgal VN, Srivastava G, Sardana K. *Int J Dermatol* 2004;43:39–47.

Note: PUVA, psoralen plus UVA.

in forming the precise treatment strategy, but it also alleviates the anxiety of the child's carer who will be confronted with a dilemma. It is, therefore, imperative to arrive at a probable diagnosis based on the salient clinical features *vide supra* and relevant investigations. The differential diagnosis of erythroderma/exfoliative dermatitis in infants and children is intricate, bizarre, and extensive. Common causes of the disease should be considered in the first instance, and it is worthwhile to recapitulate atopic dermatitis, seborrheic dermatitis, toxicity/drug reactions, and infections as the most common causes of erythroderma.^{1,2,59,88}

There are no specific approaches or therapies for managing idiopathic erythroderma. For many patients, skin care methods (i.e. wet dressing), and symptomatic treatments with oral antihistamines and topical corticosteroids provide adequate treatment. In case patients do not respond to topical therapies, they can be empirically treated through the administration of systemic corticosteroids or other immunosuppressants (e.g., methotrexate, cyclosporine); however, there are only limited data in the literature supporting the efficiency of treatments with systemic corticosteroids or other immunosuppressant in erythroderma patients. In idiopathic erythroderma patients who do not respond well to topical treatments, systemic corticosteroids are more effective than methotrexate and cyclosporine, because the former acts more rapidly. The recommended dose for prednisone is 0.5 to 1 mg/kg per day for 7–10 days, up to a maximum dose of 60 mg per day. Prednisone will then be slowly reduced over the course of several weeks in order to minimize the risk of recurrence. In idiopathic patients, successive skin biopsies, laboratory tests, and imaging examinations may eventually help reveal the underlying cause of the patient's erythroderma.¹⁴

COMPLICATIONS AND PROGNOSIS

Exfoliative dermatitis is a complex disorder involving many factors, but the net outcome depends on the underlying disease. The disease course is rapid, if it results from drug allergy, lymphoma, leukemia, contact allergens, or SSSS.^{1,3,88} The disease course is gradual if it results from the generalized spread of a primary skin disease (e.g., psoriasis or atopic dermatitis).^{59,98} Drug-induced cases of exfoliative dermatitis recover completely if initial medical management is promptly undertaken.⁸⁸ Despite skilled efforts, exfoliative dermatitis can sometimes prove fatal, especially in elderly patients. Secondary infection

(sepsis from *Staphylococcus aureus*, Kaposi varicelliform eruption from varicella zoster virus) occurred in some patients.^{106,107} Dehydration, heat loss, electrolyte imbalance, temperature dysregulation, hypoalbuminemia, edema, compensatory hypermetabolism, and high-output cardiac failure are potential complications in all cases.^{14,30}

Postinflammatory hypopigmentation or hyperpigmentation may occur, especially in individuals with dark skin. Generalized vitiligo, seborrheic keratosis, or pyogenic granuloma has also been recorded after exfoliative dermatitis.^{37,38,101,108–111} Nevi and keloid formation are rare benign sequelae, as are alopecia and nail dystrophies.⁷ In initial documented studies, the recorded death rate varied from 18% to 64%^{1,59,88}; however, the mortality has been reduced due to advances in more rapid diagnosis and improved therapeutic regimens.

CONCLUSIONS

Erythroderma is one of the occasional dermatological emergency conditions. Because the patients present with similar clinical findings, the clinician needs to find out the underlying cause. To rule out paraneoplastic etiologies, appropriate laboratory workup should be performed. Multiple skin biopsies may need to be performed to rule out cutaneous lymphoma. The patients need to be hospitalized to stabilize and to obtain appropriate care and treatment.

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Acute severe bullous dermatoses

Snejina Vassileva

A variety of skin diseases may present with the appearance of blisters (Table 22.1). The skin reacts with the formation of vesicles or larger bullae to a number of external physical, chemical, and biologic insults. Adverse reactions to systemic or topically applied drugs occupy an important place in the differential diagnosis of blistering eruptions. Bullous lesions can also occur as a manifestation of systemic diseases, as is the case of the bullae seen in diabetic patients. Atypical blistering forms of several inflammatory dermatoses exist, such as bullous lichen planus, bullous morphea, or bullous mycosis fungoides. In all these cases, blistering lesions are infrequent and temporary, in contrast to a group of chronic cutaneous disorders referred to as "bullous dermatoses," where vesiculobullous lesions are the main and characteristic clinical feature.

Some bullous dermatoses are due to genetically determined loss of basic structural elements in the skin that maintain the cohesion between the keratinocytes in the epidermis, or between the epidermal layer and the dermis within the basement membrane zone (BMZ). The majority of bullous dermatoses, however, are acquired organ-specific autoimmune diseases in which the autoantibodies target structural proteins in the skin. These disorders constitute one of the major sources of morbidity and mortality in dermatology.

Acquired autoimmune bullous dermatoses are a heterogeneous group of uncommon but often debilitating diseases including pemphigus and pemphigoid groups, linear immunoglobulin A (IgA) disease, epidermolysis bullosa acquisita, and dermatitis herpetiformis. Their histologic classification is based on the level of the skin at which the cleft occurs and the mechanisms of the blistering process. Intraepidermal acantholytic blisters, characteristic of pemphigus, result from autoantibody binding to desmosomal proteins leading to functionally impaired desmosomes and acantholysis. In the pemphigoid group of diseases, the autoantibodies are directed against different components of the dermal-epidermal junction, which results in subepidermal blistering.

DIAGNOSTIC CONSIDERATIONS

Several diagnostically relevant clinical signs and symptoms can be derived from the level of the cleft formation. Intraepidermal blisters tend to be flaccid and fragile due to their thinner roof. In contrast, subepidermal blisters have a thick, "tense" roof and can remain intact even when compressed.

Autoimmune bullous dermatoses are often misdiagnosed, and sometimes the delay in their diagnosis and institution of appropriate treatment can result in death.¹ Usually, in routine dermatologic practice, a careful clinical evaluation is sufficient to differentiate the transitory blisters of bacterial, viral, or parasitic origin, or those seen in the dermatitis/eczema

group, or to orient the clinical diagnosis toward a possible immunobullous disease.

Several clinical features, such as age of onset, family history, history of exposure to hazardous factors, and known underlying systemic or other dermatologic diseases, may provide clues as to the etiology of a blistering eruption.² A further step in the clinical recognition of bullous diseases takes into consideration the lesion morphology, distribution, evolution, and presence of characteristic clinical signs, such as the Nikolsky sign (lateral pressure in the vicinity of a blistering lesion produces detachment of the epidermis) (Table 22.2).

The diagnosis of autoimmune bullous diseases, however, strictly relies on histologic and immunologic criteria, the latter being provided by the results of the application of specialized immunohistology techniques.^{3,4} Histologic examination of a biopsy specimen from an early intact vesicle would discriminate between intraepidermal and subepidermal blister formation and the underlying histopathology patterns, but direct and indirect immunofluorescence techniques are essential in the diagnosis of immunobullous diseases (Table 22.3). Direct immunofluorescence (DIF) reveals the type and location of the immunoreactants deposited in vivo in patient's skin.⁵ It is performed on biopsy specimens from normal-appearing skin or mucosa immediately adjacent to a bullous lesion (perilesional skin). In pemphigus, DIF shows a typical diagnostic net-like epithelial staining pattern resulting from deposition of IgG on the epithelial cell surface. A linear pattern of immunoglobulin and/or complement deposition at the BMZ points to the diagnosis of the subepidermal blistering diseases, including for the pemphigoid group, linear IgA disease, epidermolysis bullosa acquisita, and bullous systemic lupus erythematosus (SLE). DIF performed on patient's skin that has been separated at the lamina lucida by incubation in a 1 M solution of NaCl allows further discrimination between the various subepidermal blistering diseases characterized by immune deposits in the lamina lucida or in the sublamina densa region. Staining of the epidermal side ("roof") of the artificial blister is suggestive of bullous pemphigoid and cicatricial pemphigoid, whereas the dermal staining ("floor" pattern) is observed in epidermolysis bullosa acquisita, bullous SLE, and anti-laminin 332 pemphigoid.

Serum antibodies are detected by indirect immunofluorescence, by Western immunoblot, or enzyme-linked immunosorbent assay (ELISA). Indirect immunofluorescence (IIF) is used for detecting circulating autoantibodies in patient serum. In most cases monkey esophagus is employed as a universal substrate to detect intercellular antibodies in pemphigus or anti-BMZ antibodies in the subepidermal group of autoimmune blistering diseases.

Immunoelectron microscopy is a method combining the advantages of immunohistochemistry techniques and the

Table 22.1 Causes of Blistering*Physical/Chemical*

Friction
 Pressure ulcers (decubitus ulcers)
 Suction (vacuum) blisters
 Thermal injury (burn, freezing)
 Ultraviolet light irradiation
 Carbon monoxide poisoning
 Fracture blisters

Infectious

Impetigo contagiosa
 Bullous impetigo/staphylococcal scalded skin syndrome
 Bullous erysipelas
 Syphilis (pemphigus neonatorum)
 Herpes simplex
 Varicella-zoster
 Coxsackie (hand-foot-mouth disease)
 Dyshidrosiform tinea/Pompholyx

Parasitic

Scabies
 Insect bites

Allergic/Immunologic

Contact dermatitis
 Dyshidrosis/pompholyx
 Fixed drug eruption
 Erythema exsudativum multiforme
 Blistering drug eruptions
 Stevens–Johnson syndrome/toxic epidermal necrolysis
 Coma-induced blisters
 Bullous amyloidosis
 Bullous lichen planus
 Bullous morphea
 Bullous allergic vasculitis
 Bullous mastocytosis
 Bullous pyoderma gangrenosum
 Bullous mycosis fungoides
 Leukemic bullae
 Grover disease (transient acantholytic dermatosis)

Metabolic diseases

Porphyria (cutanea tarda, erythropoietic)
 Pseudoporphyria (can be also drug induced)
 Chronic renal failure (hemodialysis)
 Bullosis diabeticorum
 Pellagra

Autoimmune

Pemphigus
 Pemphigoid
 Linear immunoglobulin A disease
 Epidermolysis bullosa acquisita
 Bullous systemic lupus erythematosus
 Dermatitis herpetiformis

Genetic/Hereditary

Hailey-Hailey disease
 Darier disease
 Epidermolysis bullosa hereditaria
 Congenital bullous erythroderma
 Kindler syndrome
 Incontinentia pigmenti
 Hydroa vacciniforme

resolution power of electron microscopy that is used to identify the different ultrastructural binding sites of immunoglobulins and complement within the dermal-epidermal junction in the subepidermal blistering diseases.⁶ Immunoblotting and immunoprecipitation are used to identify the antigen or antigens precipitated by the autoantibodies circulating in a patient's serum.⁷ ELISA is used as a sensitive method for the detection of autoantibodies to the immunodominant epitopes in pemphigus and pemphigoid.

THERAPEUTIC CHOICES

For several decades, a variety of both local and systemic therapies has become available that can be used to treat these diseases. Although the mortality from autoimmune bullous diseases has decreased significantly during the past several decades, they still represent one cause of morbidity in dermatology, and the common causes of death are often due to the complications of the therapeutic agents used. Suppression of autoantibody production and tissue binding is a main route in treating patients with autoimmune bullous dermatoses.

Pemphigus

Pemphigus is a group of rare life-threatening autoimmune blistering diseases, characterized by the appearance of widespread bullae and erosions of the skin and mucous membranes. It is mediated by pathogenic autoantibodies against the desmosomal proteins desmoglein 1 (Dsg 1) and desmoglein 3 (Dsg 3).⁸ Because desmosomes constitute the main adhesion structure of the epidermis, binding of autoantibodies to their target antigens leads to loss of cohesion between keratinocytes and intraepithelial blister formation, called "acantholysis."

Three major variants of pemphigus are currently recognized:

- Pemphigus vulgaris
- Pemphigus foliaceus
- Paraneoplastic pemphigus

These variants differ considerably in their clinical, histologic, and immunologic features and prognosis. Pemphigus vulgaris, also known as "deep" pemphigus, is characterized by blister formation above the basal-cell layer and is associated with antibodies against Dsg 3, which is located in the lower portions of the epidermis and is found in both the skin and mucous membranes. In contrast, pemphigus foliaceus or "superficial" pemphigus is characterized by subcorneal acantholysis and antibodies against Dsg 1, which is expressed in the upper epidermal layers and is found only in the skin. Pemphigus vulgaris affects both the skin and mucous membranes, mainly the oral mucosa, whereas in pemphigus foliaceus the lesions are confined to the skin. Several subtypes of both forms of pemphigus exist.

Prior to the advent of corticosteroids in the 1950s, pemphigus had been a deadly disease with mortality rates up to 90%–100% in affected patients within 2 years of onset.⁹ The introduction of corticosteroids and immunosuppressive drugs has dramatically transformed what was almost invariably a fatal illness into one in which the mortality of which is now less than 10%.¹⁰ Despite the advances in management and improved prognosis, however, pemphigus is still regarded as a chronic

Table 22.2 Clinical Presentation and Treatment of Autoimmune Bullous Dermatoses

Disease	Patient group	Distribution	Clinical presentation	Treatment
Pemphigus				
Pemphigus vulgaris (PV)	Middle-aged, women more often affected, rarely children/adolescents	Mucous membranes: oral, esophageal, nasal, conjunctival, genitoanal Skin: predilection for the folds, chest, back, scalp	Painful mucosal erosions Flaccid fragile blisters on normal-appearing skin, erosions and crusts Nikolsky sign positive	Systemic corticosteroids in combination with adjuvant immunosuppressive agents
Pemphigus foliaceus (PF)	Sporadic: Middle-aged and elderly, both sexes equally affected Endemic PF: FS—children and young adults; Tunisian PF—young women; Northern Columbia—men	Face, scalp, upper trunk, rarely generalized (erythroderma) Endemic: generalized Pemphigus erythematosus—seborrheic areas	Superficial blisters, scaly crusted erosions, Nikolsky sign positive; mucous membranes not affected	Systemic corticosteroids in combination with adjuvant immunosuppressive agents; topical corticosteroids
Paraneoplastic pemphigus	Adults, rarely children	Mucous membranes (oral, labial, ocular), trunk, extremities, palms and soles	Polymorphic features: severe mucositis (stomatitis, conjunctivitis, etc.), palmoplantar blisters, EEM-like, BP-like, lichenoid (GVHD-like) exanthems	Treat underlying malignancy; supportive care; high-dose steroids and steroid-sparing agents
Drug-induced pemphigus	Any age, most often	See PF	PF phenotype (thiol drugs), rarely PV phenotype (nonthiol drugs)	Systemic corticosteroids in combination with adjuvant immunosuppressive agents; topical corticosteroids
Pemphigoid group				
Bullous pemphigoid	Elderly, rarely children	Flexor surfaces of upper and lower extremities, trunk, rarely localized Mucous membranes usually not affected	Tense blisters on inflamed or normal skin, and urticarial plaques, typically on the flexor surfaces of the arms and legs, lateral trunk; no mucosal involvement; elderly affected	Topical corticosteroids (clobetasol propionate) or systemic corticosteroids
Mucous membrane (cicatricial) pemphigoid (MMP/CP)	Elderly, women more often affected; rarely prepubertal girls	Mucous membranes (oral, ocular, anogenital, nasal, laryngeal, esophageal), rarely skin Vulva in childhood cases	Erosions and ulcerations (rarely blisters) of the oral or any other mucous membrane; healing with adhesions and scarring	Systemic corticosteroids in combination with adjuvant immunosuppressive agents or dapsone
Brunsting-Perry CP	Elderly men	Head and neck	Blisters, erosions, atrophic scars	

(Continued)

Table 22.2 (Continued) Clinical Presentation and Treatment of Autoimmune Bullous Dermatoses

Disease	Patient group	Distribution	Clinical presentation	Treatment
Pemphigoid gestationis	Pregnant women Women with trophoblastic tumors	Initially periumbilical, later widespread	Erythematous urticarial patches and plaques, tense vesicles and blisters.	Topical corticosteroids in combination with oral antihistamines; In severe cases systemic corticosteroids
Anti-Laminin 332 (antiepiligrin) MMP	See MMP	Mucous membranes	See mucous membrane pemphigoid (severe cases)	See mucous membrane pemphigoid
Anti-p200/Laminin γ 1 pemphigoid	Elderly, men more often affected	Trunk and extremities; oral and genital mucosae can be affected	May be BP-like, LAD-like, or DH-like; in one-third of cases associated psoriasis	Systemic corticosteroids, with or without adjuvant immunosuppressive agents or dapsone
Linear IgA dermatosis (LAD)	Preschool children or adults above 60 years old	Flexor surfaces, trunk, perineum, face; oral mucosa often involved	Tense blisters on erythematous skin, pruritic annular plaques with blisters at the periphery of resolving lesions ("string of pearls" sign)	Dapsone in combination with topical corticosteroids
Epidermolysis bullosa acquisita (EBA)	Middle-aged, women slightly more often	Trauma-prone sites—hands, feet, elbows, knees, mucous membranes, nail involvement	Classical: skin fragility, trauma-induced blisters healing with atrophy and milia; onycholysis, nail dystrophy Inflammatory: similar to BP, MMP, Brunsting-Perry CP, or LAD; sometimes combined features of classical phenotype	Systemic corticosteroids in combination with adjuvant immunosuppressive agents
Bullous systemic lupus erythematosus (BSLE)	Young adults, women more often affected (Afro-American)	Upper part of trunk, supraclavicular regions, proximal extremities, neck, face	Widespread, pruritic, nonscarring blistering eruption, often starting with blisters on lip vermilion; rarely phenotype of classical EBA	Dapsone monotherapy or in combination with systemic corticosteroids
Dermatitis herpetiformis (DH)	Young adults and children or elderly; men slightly more often affected	Extensor surfaces of the limbs, elbows, knees, buttocks, back, shoulders, face and scalp	Grouped pruritic papules and vesicles, hemorrhagic crusts; associated GSE	Dapsone or sulfapyridine; GFD

Notes: GFD, gluten-free diet; GSE, gluten-sensitive enteropathy; GVHD, graft versus host disease.

Table 22.3 Molecular, Histologic and Immunofluorescence Findings in Autoimmune Bullous Dermatoses

Disease	Histology findings	Target antigens	DIF	IIF/split skin substrate
Pemphigus				
Pemphigus vulgaris (PV)	Intraepidermal suprabasal acantholysis, “tombstoning” of basal keratinocytes	Dsg 3, Dsg 1, Dsg 4, plakoglobin, E-cadherin, acetylcholine receptor, Dsc 1-3	Intercellular IgG and C3 in the epidermis	Intercellular IgG abs on monkey esophagus
<i>P. foliaceus</i> (PF) Seneear-Usher syndrome	Subcorneal acantholysis	Dsg 1, plakoglobin	See PV Lupus band (IgG, IgM, C3) at the BMZ	See pemphigus vulgaris ANA on monkey esophagus or Hep-2
Paraneoplastic pemphigus	Interface dermatitis, keratinocyte necrosis, dyskeratosis, lichenoid infiltrate in the dermis	Dsg 3, envoplakin, periplakin, desmoplakin 1 and 2, A2ML1, BP230, plectin, Dsg 1	Intercellular IgG and C3 in the epidermis; linear IgG and/or C3 at the BMZ	Intercellular IgG abs on monkey esophagus and on plakine rich (rat urinary bladder)
Pemphigoid group				
Bullous pemphigoid (BP)	Subepidermal bulla with inflammatory eosinophil-predominant infiltrate, also containing lymphocytes and neutrophils.	BP180 NC16A BP230	Linear deposits of IgG and/or C3 at the BMZ	Circulating IgG anti-BMZ antibodies—epidermal pattern
Mucous membrane pemphigoid (MMP)	Subepithelial bulla with or without inflammatory infiltrate	BP180 NC16A, $\alpha 6\beta 4$ integrin, laminin 311, BP230	See BP	Circulating IgG anti-BMZ antibodies—epidermal or mixed pattern
Pemphigoid gestationis	See BP	BP180 NC16A, BP230	Linear deposits of C3 (IgG only rarely) at the BMZ	Circulating IgG anti-BMZ antibodies—epidermal pattern; HG factor
<i>Anti-Laminin 332 (antiepiligrin) MMP</i>	Subepidermal bulla with sparse superficial lymphohistiocytic infiltrate with neutrophils and/or eosinophils	Laminin 332	See BP	Circulating IgG anti-BMZ antibodies—dermal pattern
<i>Anti-p200/Laminin $\gamma 1$ pemphigoid</i>	Subepidermal bulla with superficial neutrophil-predominant infiltrate	Laminin- $\gamma 1$	See BP	Circulating IgG anti-BMZ antibodies—dermal pattern
Linear IgA dermatosis (LAD)	Subepidermal bulla with inflammatory, neutrophil- or eosinophil predominant infiltrate.	LAD-1 Type VII collagen	Linear deposits of IgA and C3 at the BMZ	Circulating IgA anti-BMZ antibodies—epidermal, dermal, or mixed pattern
Epidermolysis bullosa acquisita (EBA)	Classical EBA: Subepidermal bulla with sparse mononuclear cell infiltrate; Inflammatory EBA: Subepidermal bulla with mixed, neutrophil predominant infiltrate	Type VII collagen	Linear deposits of IgG and C3 at the BMZ, rarely IgA and IgM	Circulating IgG anti-BMZ antibodies—dermal pattern
Bullous systemic lupus erythematosus (BSLE)	Subepidermal vesicle, indistinguishable from dermatitis herpetiformis; sometimes leukocytoclastic vasculitis	Type VII collagen	Linear or granular deposits of IgG and C3 at the BMZ; rarely IgA and IgM	Circulating IgA anti-BMZ antibodies—epidermal, dermal, or mixed pattern
Dermatitis herpetiformis (DH)	Subepidermal bulla with neutrophil microabscesses in dermal papillae	Epidermal transglutaminase	Granular deposits of IgA and C3 along the BMZ, more intensive at the tips of the dermal papillae	IgA antiendomysial antibodies on monkey esophagus substrate

Note: BMZ, basement membrane zone; DIF, direct immunofluorescence; IIF, indirect immunofluorescence; HG, herpes gestationis.

debilitating condition, in which the patient's life is mainly endangered by the complications and side effects of the long-term treatment and not by the disease itself.

Pemphigus vulgaris is the most common and one of the most severe forms of pemphigus that still carries a grave prognosis. Although people from all races can be affected,

pemphigus vulgaris is more prevalent in some ethnic groups (Ashkenazi Jewish, Japanese), and in some regions, such as the Mediterranean and Balkan countries.¹¹ Individuals with certain human leukocyte antigen (HLA) allotypes are predisposed to the disease, although the susceptibility gene differs depending on ethnic origin¹²; thus, HLA-DRB1*0402 is associated with the



Figure 22.1 Painful erosions on the lip mucosa in a patient with pemphigus vulgaris.

disease in Ashkenazi Jews and DRB1*1401/04 and DQB1*0503 in non-Jewish patients of European or Asian descent.

Pemphigus vulgaris most often affects middle-aged adults with a preponderance for women. In the majority of cases, the disease starts from the oral mucosa and nasopharynx and in 50%–60% of patients may remain localized to these sites for months. Flaccid blisters that easily rupture by leaving painful erosions are characteristic of the mucosal variant of pemphigus vulgaris (Figure 22.1). The erosions show little or no tendency to heal, which results in decreased food intake and progressive loss of weight. There is usually a characteristic *foetor ex ore*. Other mucous membranes, such as the conjunctiva, esophagus, and genital and anal mucosa, may be involved.

Within various periods of time, cutaneous involvement develops characterized by the appearance of flaccid, peripherally extending bullae, arising on unchanged skin. The flexural areas, back, abdomen, face, and scalp are most often affected (Figure 22.2). If left untreated, the disease shows a progressive course with appearance of new bullous lesions and involvement of larger areas of skin. Individuals younger than 18 years



Figure 22.2 Pemphigus vulgaris: few flaccid blisters on normal skin and large erosions partially covered by crusts.

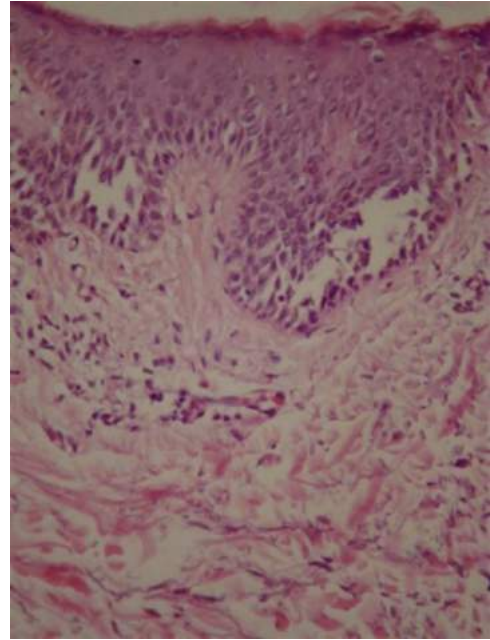


Figure 22.3 Acantholysis with suprabasilar clefts in pemphigus vulgaris. Few acantholytic cells floating in the blister cavity.

can be rarely affected (childhood or adolescent pemphigus).¹³ In the pediatric population, the disease has a similar course to that in adults.

Histopathologically, pemphigus vulgaris is characterized by acantholytic intraepidermal blister formation above the basal layer of keratinocytes (Figure 22.3). The immunologic hallmark of pemphigus vulgaris is the demonstration of *in vivo* bound and circulating IgG autoantibodies against the cell surface of keratinocytes. DIF reveals deposits of IgG in the intercellular spaces of the epidermis, a diagnostic staining pattern found in practically all patients with active disease (Figure 22.4).

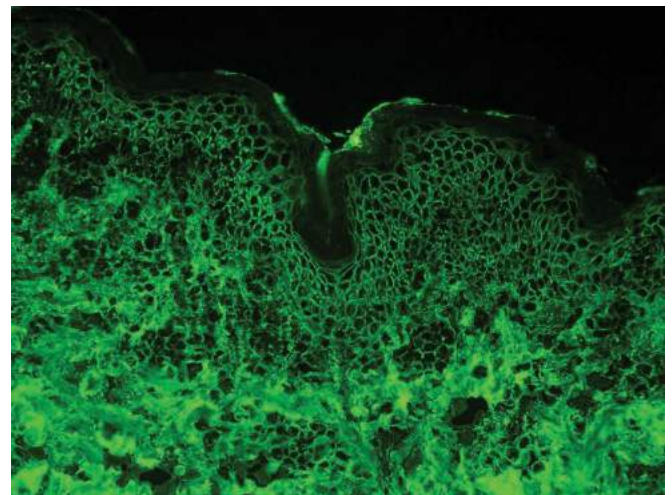


Figure 22.4 Direct IF on perilesional skin in pemphigus: intercellular fluorescence pattern with IgG throughout the epidermis.

The presence of circulating autoantibodies can be detected and measured using various immune serology assays, including IIF, immunoblotting, and ELISA. IIF reveals serum IgG antibodies, which produce the characteristic intercellular epithelial staining on monkey esophagus (or human esophagus) as a substrate (Figure 22.5). Their titers correlate with the activity of the disease. Immunoblot analysis can detect autoantibody profiles that have been defined to be specific for each clinical phenotype of pemphigus.^{14,15}

Pemphigus vegetans is a rare clinical form of pemphigus vulgaris (1%–2% of patients) affecting the skin folds,¹⁶ where long-lasting refractory erosions are transformed into hypertrophic, papillomatous, or verrucous vegetating lesions (Figure 22.6). The coexistence of pemphigus vegetans and various internal malignancies has been reported in the literature.¹⁷

Pemphigus foliaceus is a rare variant of pemphigus, characterized by subcorneal epidermal blisters and pathogenic IgG anti-Dsg1 autoantibodies.¹⁸ Clinically, pemphigus foliaceus manifests with transient cutaneous superficial blisters that are fragile to the point that often only scaly, crusted erosions with erythema are found on physical examination (Figure 22.7). Lesions are typically in a seborrheic distribution—the central portion of the face, head, neck, and upper torso. Most often the disease remains localized for several years but may progress



Figure 22.6 Neumann type of pemphigus vegetans: vegetations arise at the places of persisting erosions, usually located in the skin folds.

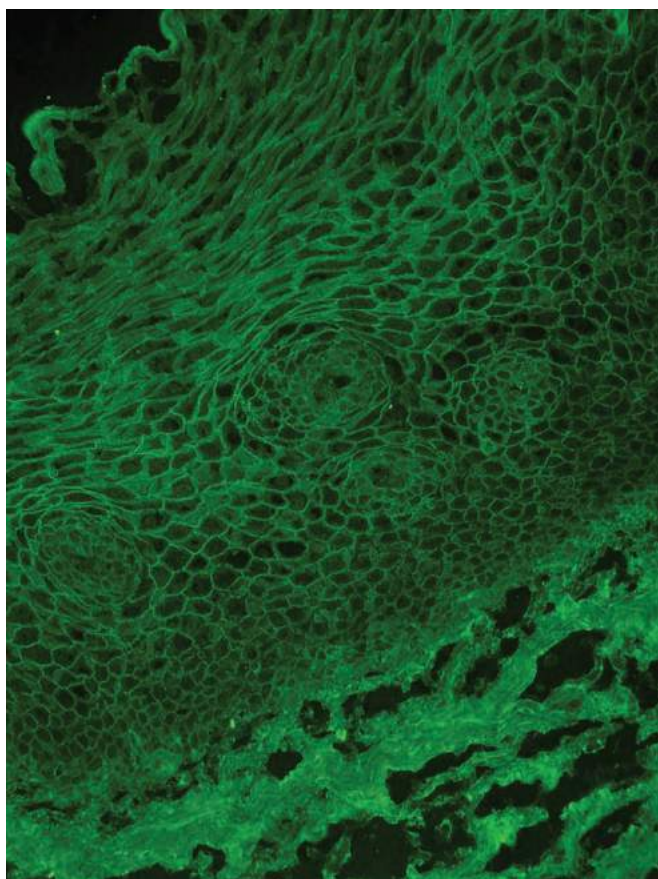


Figure 22.5 Indirect IF with pemphigus serum on human esophagus substrate: binding of IgG antibodies on the epithelial cell surface (network epidermal fluorescence).

to erythroderma. The fact that the mucous membranes are not affected is an important clinical feature that differentiates pemphigus foliaceus from pemphigus vulgaris.¹⁹

An endemic subtype of pemphigus foliaceus, known as *fogo selvagem* (from the Portuguese “wild fire”), exists in certain regions of Brazil and other countries of South America.²⁰ Endemic pemphigus foliaceus differs from the nonendemic form of the disease in its geographic distribution, high familial incidence, and younger age of onset²¹; a higher incidence of severe generalized exfoliative forms is related to a greater morbidity and mortality in fogo selvagem. An endemic form of pemphigus foliaceus has also been recently described in Colombia²² and Tunisia.²³ The endemic nature of the condition



Figure 22.7 Nonendemic pemphigus foliaceus: scaly, oozing erythematous plaques and superficial erosions on the face.

is thought to be precipitated by an immune response to an environmental antigen(s), currently not yet identified.

Pemphigus erythematosus, also referred to as pemphigus seborrhoicus, or Senear-Usher syndrome, is a rare subtype of pemphigus foliaceus that combines clinical and immunopathologic features of pemphigus and cutaneous lupus erythematosus (LE), involving the scalp, face, upper portions of the chest, and back. The facial lesions may show the typical butterfly distribution characteristic of SLE.

Paraneoplastic pemphigus (PNP) is the most severe variant of the disease, occurring in association with malignancies, mainly of B-cell lymphoproliferative origin. It was defined in 1990 on clinical, histologic, and immunologic criteria.²⁴ The autoantibody response in PNP is directed against a complex of desmosomal proteins.^{25–27} Clinical manifestations of PNP combine features of pemphigus, erythema multiforme, or Stevens–Johnson syndrome, pemphigoid, and lichen planus. A major clinical feature includes severe involvement of multiple mucous membranes. The cutaneous lesions are polymorphic and may consist of flaccid but also tense blisters, morbilliform exanthema, lichenoid, or psoriasiform changes, as well as palmoplantar target lesions.²⁸ By IIF, PNP antibodies react with the simple, columnar, and transitional epithelial tissue substrates (rat bladder substrate) in addition to the stratified squamous epithelium (Figure 22.8).²⁹

Approximately 80% of reported cases with PNP are linked to non-Hodgkin lymphoma, chronic lymphatic leukemia, and Castleman disease; less commonly Waldenström macroglobulinemia, T-cell lymphoma, thymoma, Hodgkin disease, retroperitoneal sarcoma, reticulum cell sarcoma, round-cell liposarcoma, and inflammatory fibrosarcoma have been described.^{30,31} There are isolated reports of associations with solid cancers.³² The mortality rate in PNP is estimated to be more than 90%. Death is usually secondary to sepsis, gastrointestinal bleeding, multiple organ failure, or respiratory failure. Respiratory failure with features of bronchiolitis obliterans occurs in approximately 30% of patients.³³ Recently, the term “paraneoplastic autoimmune multiorgan syndrome” (PAMS)

has been introduced to encompass the aggregate of signs and symptoms associated with the distinct morbid process affecting the skin, mucosa, and lungs in a heterogeneous group of patients with PNP/PAMS.^{31,34}

Drug-induced pemphigus, first recognized half a century ago, is attributed mainly to molecules that contain a thiol (–SH) group, such as D-penicillamine, captopril, and thiopronine, or a disulfide bond that readily releases SH groups, such as penicillin and cephalosporins.³⁵ These drugs possess powerful acantholytic qualities in vitro.³⁶ Other drugs known to induce pemphigus contain an active amide group in their molecule.³⁷ In some cases, the disease may disappear when the drug is withdrawn (drug-induced pemphigus), but it usually continues even after removal of the initiating agent (drug-triggered pemphigus). Some cases of pemphigus have been described after occupational contact with pesticides, which led to the description of “contact pemphigus,” as a variant of environmentally induced disease.^{38,39}

Pemphigus has also been reported in association with several other autoimmune diseases, including systemic lupus erythematosus (SLE), myasthenia gravis, rheumatoid arthritis, and BP.^{40,41}

Systemic corticosteroids are the mainstay of treatment for pemphigus. Usually prednisolone is administered at a dose of 1–2 mg daily, with or without other immunosuppressive agents, and is continued until there is cessation of appearance of new blistering lesions and healing of the majority of erosions. The dosage is then reduced by one half until all of the lesions have cleared, followed by tapering to a minimum effective maintenance dosage. Because the disease has a chronic course, patients receiving long-term corticosteroid therapy frequently have serious side effects. Alternative or adjuvant therapies for patients who do not respond to or who experience complications from corticosteroids include immunosuppressive agents such as cyclophosphamide, azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil, and immunomodulatory drugs and procedures such as dapsone, gold salts, and plasmapheresis. Administration of high-dose intravenous immunoglobulins (2 g/kg/month) has been successfully employed in cases of pemphigus unresponsive to conventional immunosuppressive treatment.⁴² Recently, a single cycle of rituximab, a monoclonal antibody directed against the CD20 antigen of B lymphocytes, has been demonstrated to effectively control severe pemphigus, but the potential long-term risks of this treatment need to be further assessed.⁴³

Even with the use of corticosteroids and other immunosuppressive agents, there is still significant morbidity and mortality associated with pemphigus. A common cause of death is infection secondary to the immunosuppression required to treat the disease. Most deaths occur within the first few years of the disease. Unfortunately, many of the drugs used to treat this disease have serious side effects, and patients must be monitored closely for infection, renal and liver function abnormalities, electrolyte disturbances, hypertension, diabetes, anemia, and GI bleeding.⁴⁴

AUTOIMMUNE SUBEPIDERMAL BULLOUS DERMATOSES

Autoimmune subepidermal blistering dermatoses include the pemphigoid group of diseases, linear IgA dermatosis, epidermolysis bullosa acquisita, and dermatitis herpetiformis. They are characterized by circulating and tissue-bound

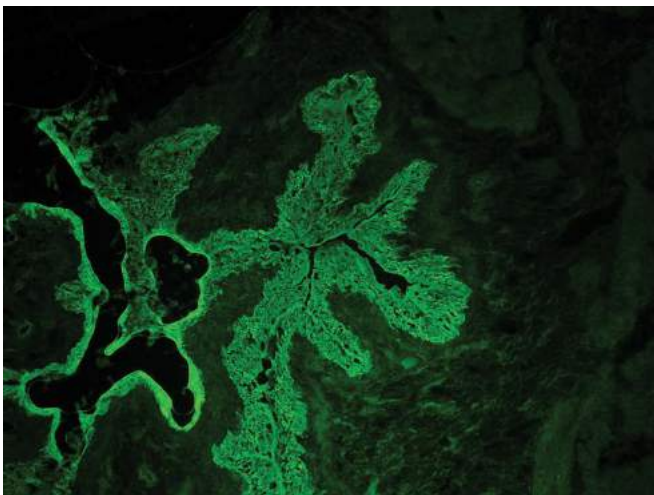


Figure 22.8 Indirect IF of serum from a patient with paraneoplastic pemphigus: intercellular staining of rat urinary bladder epithelium as a substrate.

autoantibodies against various components of the dermoepidermal anchoring complex.⁴⁵ Anchoring complexes are specialized focal attachment sites within the cutaneous BMZ that play a crucial role in dermoepidermal adhesion. Antibody binding to various proteins within this complex results in dermoepidermal separation and tense blister formation. The dermoepidermal anchoring complex consists of hemidesmosomes of the basal keratinocytes, anchoring filaments of the basement membrane, and anchoring fibrils of the papillary dermis. Different structural proteins within this complex are recognized as autoantigens in various acquired autoimmune subepidermal bullous diseases. Recent advances in the molecular characterization of BMZ components have led to a better understanding of the interaction between these molecules as well as the autoimmune response against these proteins.

Pemphigoid Group

The pemphigoid group of autoimmune bullous dermatoses is characterized by the production of autoantibodies targeting adhesion molecules that are part of the hemidesmosomes at the dermal-epidermal junction. Their immunohistological hallmark is the formation of subepidermal blister and deposits of immunoreactants, usually IgG (more rarely IgA and IgE) and complement, along the BMZ. The pemphigoid group of bullous dermatoses comprises bullous pemphigoid, mucous membrane (cicatricial) pemphigoid, pemphigoid gestationis, and lichen planus pemphigoides. Other recently identified rare forms of pemphigoid include anti-laminin 332 pemphigoid and p200 pemphigoid.

Bullous Pemphigoid

Bullous pemphigoid (BP) is an acquired subepidermal autoimmune bullous disease typically affecting elderly individuals older than 60 years. In 1953,⁴⁶ BP was first described as a separate disease from pemphigus vulgaris, and later studies in 1967⁴⁷ revealed the presence of in vivo bound and circulating autoantibodies directed against the BMZ of stratified epithelia. Two hemidesmosomal proteins, the BP antigen 230 (BP230), also termed BP antigen 1 (BPAG1), and the BP antigen 180 (BP180), also termed BP antigen 2 (BPAG2) or type XVII collagen, have been identified as the targets of the autoantibodies in BP.^{48,49} A passive-transfer mouse model of BP strongly suggests that antibodies directed against the BP180 protein are of primary pathogenic importance in the development of the disease. The antibody-antigen interaction, local activation of complement, and release of cytokines lead to loss of dermoepidermal adherence and formation of subepidermal blisters.⁵⁰

BP is believed to be the most common autoimmune blistering disease in Western European countries, with an estimated incidence of six to seven cases per 1 million population per year in France⁵¹ and Germany⁵² and even higher in the United Kingdom.⁵³ The disease appears to be more rare in the Far East.⁵⁴ Historically, BP has been thought to be of better prognosis than pemphigus.⁵⁵ Over the past decade, however, several large European studies demonstrated that even with treatment, patients with BP have a prognosis as grim as a diagnosis of end-stage heart disease, with more than 40% of patients dying within 12 months.^{56–58} Much of the mortality may be related to the age and the general condition of patients. In a retrospective study from Scotland, 48% of patients with BP died within 2 years of diagnosis, particularly from respiratory diseases.⁵⁹ Treatment with corticosteroids and other immunosuppressive

agents may also play a role. It has been suggested that patients with circulating antibodies to BPAG2 tend to have a poorer prognosis due to a more severe disease requiring higher doses of systemic steroids.^{60,61}

Clinically, BP is characterized by a polymorphic eruption consisting of tense blisters on erythematous or normal-appearing skin, urticaria-like patches and plaques, and eczematous plaques. Usually, the eruption is intensely pruritic.⁶² The eruption is usually widespread, with a predilection for the flexural surfaces of the arms and legs (Figure 22.9), lower abdomen, and the lateral aspects of the trunk. Rarely, BP may occur in children.⁶³

Association of BP with a variety of other autoimmune disorders has been observed, but evidence through large controlled studies for such an increased incidence has not revealed a relationship.⁶⁴ In some cases, BP has been thought to be induced by physical injury (burn, radiotherapy, or ultraviolet irradiation)⁶⁵ or by systemic or topical medications.

The diagnosis of BP relies on the histologic findings of subepidermal blistering, accompanied by eosinophilic infiltration in the superficial dermis and on the results of IF testing. Linear IgG and C3 deposition at the BMZ are observed on DIF of perilesional skin (Figure 22.10). IIF reveals circulating IgG anti-BMZ antibodies in patients' serum that react with the epidermal side of 1 M NaCl split skin as a substrate (Figure 22.11). Autoantibodies against the NC16A domain of BP180 are identified by ELISA.

Treatment of BP consists of corticosteroids, administered at lower doses (0.5–0.75 mg/kg/day) than those used to treat pemphigus, alone or in combination with steroid-sparing agents such as azathioprine, mycophenolate mofetil, or tetracycline. Methotrexate may be used in patients with severe disease, who are unable to tolerate prednisone. Plasma exchange therapy may be considered in refractory cases. Because most morbidity and mortality are secondary to treatment, there is now a tendency to treat patients with potent topical corticosteroids. The disease is self-limited, and approximately one-half of treated cases will remit within 6 years.⁴⁵



Figure 22.9 Bullous pemphigoid: tense blisters on inflammatory background, involving the flexural surfaces of the lower extremities.

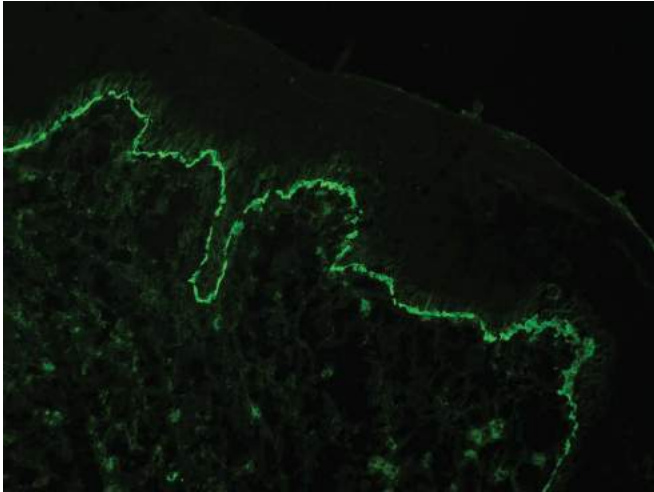


Figure 22.10 Bullous pemphigoid: direct IF on perilesional skin showing linear C3 at the BMZ.

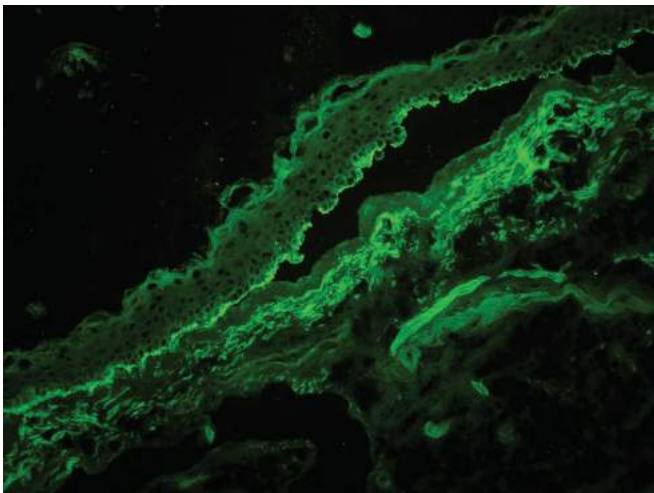


Figure 22.11 Bullous pemphigoid: indirect IF on salt-split skin substrate reveals binding of antibodies to the roof of the blister.

Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP), also known as cicatricial pemphigoid (CP), is a rare but well-defined variant of pemphigoid, characterized by erosive, scarring subepidermal blistering lesions of mucosal surfaces and less often, the skin. Depending on the mucosal surface that is mainly affected, patients with MMP may first present to the ophthalmologist, dermatologist, dentist, gastroenterologist, gynecologist, otolaryngologist, or even to the primary care physician.

The oral mucosa is almost always affected, followed by other mucosae (eye, nose, pharynx, larynx, esophagus, genitalia, anus). Desquamative gingivitis is the most common oral manifestation, but nonhealing ulcers on the buccal mucosa or the soft and hard palates are not rare. Bullae quickly rupture, leaving slowly healing erosions, followed by scarring and

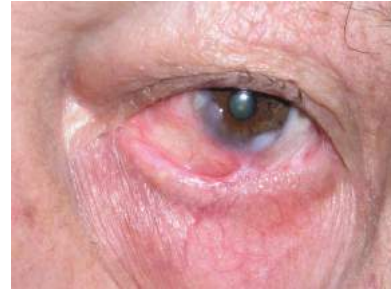


Figure 22.12 Ocular mucous membrane pemphigoid: conjunctival erosions on the lower lid with multiple synechiae.

adhesions between the various structures of the oral cavity involved. Laryngeal involvement may lead to a sore throat, hoarseness, and possible loss of speech. Supraglottic stenosis secondary to erosions, scarring, and edema may necessitate a tracheostomy as the airway is further compromised. Esophageal erosions and scarring can lead to the formation of strictures, with dysphagia, odynophagia, and weight loss.

Ocular MMP is characterized by erythema, pain, tearing, and photophobia. The inflammatory lesions are followed by progressive subconjunctival cicatrization, resulting in decreased vision, photosensitivity, scarring (Figure 22.12), fibrosis, and in severe cases, blindness. The course of the disease is usually slow but progressive and may be punctuated by periods of explosive inflammatory activity. There is a 2:1 preponderance for women; the average age of onset of MMP is reported to be 65 years, but this does not take into account the observation that most cases of MMP are relatively advanced at the time of diagnosis.⁶⁶

A less frequently encountered variant of CP, referred to as Brunsting-Perry pemphigoid, is characterized by vesiculobullous lesions and scarring confined to the head and neck areas.⁶⁷

Pemphigoid Gestationis

Pemphigoid gestationis (PG), previously known as “herpes gestationis” (HG), is a pregnancy-specific autoimmune subepidermal blistering dermatosis that usually develops in the second or third trimester and clinically presents with severely pruritic urticarial lesions that progress to large tense bullae. The estimated incidence of the disease ranges between 1 in 10,000 and 1 in 50,000 pregnancies,⁶⁸ with only 14% of the cases developing postpartum.⁶⁹ The fetal prognosis is dominated by the risk of prematurity and small fetal weight.

The exact pathogenesis of PG is still largely unknown, but it has been postulated that the disease is primarily related to an allogeneic reaction against the fetoplacental unit, triggered by an aberrant expression of major histocompatibility complex class II molecules in the placenta. The result is an autoimmune response directed against the chorioamniotic cells but cross-reacting with BPAG2 in the skin. Hormonal factors have also been implicated in the pathogenesis of the disease as flares have been reported with menses or use of oral contraceptives.

Linear IgA Disease

Linear IgA disease (LAD) is a subepidermal autoimmune blistering disease defined by the presence of linear deposits of IgA

at the BMZ. It was first recognized as a separate entity from dermatitis herpetiformis (DH) in 1979,⁷⁰ based on the finding of in vivo bound IgA anti-BMZ antibodies and the lack of an associated gluten-sensitive enteropathy (GSE). Currently, there is compelling evidence that the IgA autoantibodies in LAD are directed against heterogeneous antigen targets in the BMZ and ultrastructurally localize to the lamina lucida, anchoring fibrils, or the lamina densa.⁷¹

LAD can occur at any age, but there are two peaks of onset: in adults between 40 and 60 years old, and in children of preschool age. The estimated incidence of LAD in studies from Western Europe varies from 0.22 to 0.5 per million.^{72–74} It has been reported to be more common in women than in men.⁷⁵

The clinical manifestations of LAD include a widespread pruritic blistering eruption, predominantly involving the lower part of the trunk and the extremities, especially the inner portion of the thighs and the pelvic region, and frequent mucous membrane involvement. The lesions tend to form the “cluster of jewels” or “string of pearls”—that is, annular papules, urticarial plaques, vesicles and bullae which develop with a tendency to heal in the center (Figure 22.13).

Although the majority of cases of LAD are “idiopathic,” there have been a number of triggering factors reported, including trauma, ultraviolet exposure, infections, and a wide range of drugs, such as vancomycin, penicillin, antiepileptics, captopril, diclofenac, and sulfonamides.⁷⁶ Drug-induced LAD tends to resolve after discontinuation of the offending drug and is associated with a lower morbidity⁷⁷; however, some more severe cases mimicking erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis have been described.⁷⁸ Other important systemic associations of LAD include other autoimmune diseases, such as inflammatory bowel disease, SLE, dermatomyositis, rheumatoid arthritis, and acquired hemophilia. Besides, a relationship between LAD and various malignant diseases has been reported, including lymphoproliferative malignancies as well as solid visceral neoplasms.⁷⁹

The diagnosis of LAD is based on the histology, which invariably shows a subepidermal blister with a superficial

dermal infiltrate of neutrophils, and on the DIF finding of linear IgA along the BMZ. The IIF of patient’s serum can be either negative or detect low levels of IgA anti-BMZ antibodies that would react with the epidermal, dermal, or both sides of the blister, when tested on saline-separated skin as a substrate.

The aim of treatment in LAD is suppression of disease activity with the minimum treatment possible. In the majority of cases, there is spontaneous remission between 3 and 6 years after the onset; therefore, it is important not to overtreat the disease. Dapsone is the therapy of choice in managing LAD. Immunosuppressive agents have been used with variable success. Successful use of IV immunoglobulin therapy has been reported in patients with progressive LAD unresponsive to dapsone and systemic corticosteroids.⁸⁰

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita (EBA) is a rare acquired autoimmune blistering disease characterized by subepidermal blisters and tissue-bound and circulating antibodies directed against sublamina densa of the epithelial basement membranes.⁸¹ The patient’s antibodies recognize type VII collagen, which is the major constituent of anchoring fibrils, the structures that connect lamina densa of the BMZ to the papillary dermis.⁸² EBA was first described by George T. Elliot (1855–1931)⁸³ more than 100 years ago as an acquired form of epidermolysis bullosa, with clinical features highly reminiscent of the inherited forms of dystrophic epidermolysis bullosa (EB), in which an inherited mutation in the gene encoding for type VII collagen results in paucity of anchoring fibrils and skin fragility. Similarly to the hereditary dystrophic EB, EBA is characterized by blistering, scarring, and milia formation at trauma-prone areas (Figure 22.14). In addition to this “classical” mechanobullous form, there are several inflammatory subtypes of EBA that can be clinically indistinguishable from BP, MMP, or LAD.^{84–87}

The incidence of EBA ranges from 0.2 to 0.5 new cases per million per year.^{88–90} It appears that it is slightly more common



Figure 22.13 Adult linear IgA dermatoses: annular lesions with tense blisters at the periphery (“cluster of jewels” sign).



Figure 22.14 Classical epidermolysis bullosa acquisita: atrophy and milia are observed at the sites of healing mechanobullous lesions.

in women and in patients of color.⁹¹ The mean age of onset is in the fourth decade although children and elderly over 70 years old may also be affected.⁹²

EBA is a chronic disease that is difficult to treat and for which there is no cure.⁹³ It is associated with significant morbidity, resulting from involvement of various skin and mucosal surfaces. In patients with MMP-like EBA the involvement of the mucous membranes can result in irreversible complications similar to those seen in CP, including blindness and esophageal strictures. There may be tracheal involvement and upper airway obstruction requiring tracheotomy.

EBA has been reported in association with a number of other autoimmune and systemic diseases,⁹⁴ the most frequent of which being inflammatory bowel disease.⁹⁵ A recent study showed that sera from patients with Crohn disease reacted by immunoblot analysis with type VII collagen, which exists in both the skin and the gut.⁹⁶ In addition, paraneoplastic cases of EBA have been reported.⁹⁷

The diagnosis of EBA relies on the constellation of clinical, histologic, and immunologic data. The DIF on perilesional skin reveals linear deposits of IgG and C3 at the BMZ. Approximately 10%–30% of patients have circulating IgG anti-BMZ antibodies that bind to the dermal side of a salt-split skin substrate (Figure 22.15). By immunoblotting EBA, autoantibodies bind to 290 and 145 kd proteins, which represents the full-length alpha chain of type VII collagen or its amino-terminal globular NC1 domain, respectively. A sensitive ELISA test for the detection of autoantibodies to type VII collagen using recombinant protein is also available.⁹⁸

Treatment for EBA is challenging and often unsatisfactory. Mild cases follow a chronic course, whereas aggressive disease is often difficult to control and is associated with a significant mortality rate. Systemic corticosteroids, used as standard treatment for EBA, often in combination with cyclophosphamide, azathioprine, or methotrexate, may be ineffective in some cases. Some therapeutic success has been reported with colchicine, dapsone, photopheresis, infliximab, or high-dose intravenous immunoglobulin.⁹⁹

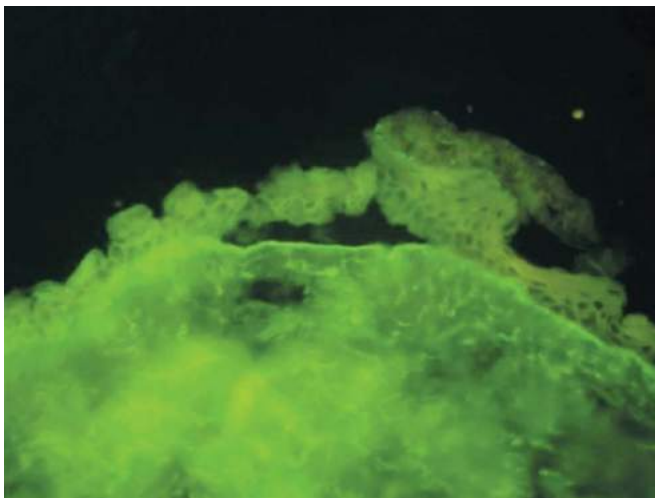


Figure 22.15 Epidermolysis bullosa acquisita: indirect IF on salt-split skin substrate reveals binding of antibodies to the floor of the blister.

Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is an uncommon subepidermal blistering disease, characterized by an intensely pruritic cutaneous eruption, typical IF findings, and association with GSE. Since its initial description in 1884 by Louis A. Duhring (1845–1913),¹⁰⁰ DH has been confounded for decades with BP under the term *Duhring-Brocq disease*. Beginning in the 1960s to 1970s, however, several clinical and IF features, typical for DH and not found in other immunobullous diseases, were identified that led to the current concept of DH as a distinct immunobullous disorder, strongly related to celiac disease (CD) in the spectrum of the gluten-sensitive disorders.^{101–103} DH and CD have a common immunogenetic background, sharing a strong association with certain major histocompatibility complex antigens, such as HLA-B8, HLA-DR3, and HLA-DQw2. First-degree relatives of patients with DH frequently develop CD. Immunohistologically, DH is characterized by granular deposits of IgA and complement C3 in the papillary dermis of uninvolved skin.¹⁰⁴ Epidermal and tissue transglutaminases are the major autoantigens recognized in the skin lesions of DH and targeted by the circulating IgA antibodies to endomysium (intermyofibril substance of smooth muscle) found in the serum of patients with DH and CD.^{105,106} All recent data related to the pathophysiology of DH indicate that epidermal transglutaminase (eTG), also known as transglutaminase 3 (TG3), is the main autoantigen in DH and patients with DH have IgA antibodies specific for TG3 and IgA antibodies that react with both TG3 and tTG.¹⁰⁷ It is now well known that TG3 in DH skin is found in the papillary dermis and overlaps with the same sites of IgA deposition.¹⁰⁸

Clinically, DH presents with an itchy polymorphic cutaneous eruption consisting of excoriated erythematous papules and vesicles, often grouped in a herpetiform pattern (Figure 22.16). The lesions have a typical symmetrical distribution over the extensor surfaces, including elbows, knees, shoulders, sacrum, and buttocks. The onset of DH is usually in the second or third decade, but may occur at any age. A diet overloaded with gluten or iodides (seafood) can often precipitate a flare of the eruption. The eruption runs a chronic course, with flares



Figure 22.16 Dermatitis herpetiformis: symmetric pruritic polymorphic eruption involving the elbows and extensor forearms.

and remissions, especially if unrecognized or left untreated. Patients from both genders may be affected, but there seems to be a slightly higher male preponderance.

DH and CD show an uneven geographic distribution, with higher incidence rates in Europe or in populations with European descent. In a study from Finland, the incidence was 3.5 per 100,000 per year.¹⁰⁹ In contrast, DH is extremely rare in Asians and Afro-Caribbeans.¹¹⁰ Morbidity in DH is mainly related to the intense pruritus, scratching, discomfort, and insomnia, as well as to the risk of superimposed bacterial or viral infections. Systemic complications are associated with the GSE, which is present in practically all patients with DH, despite the fact that most of them may have only subclinical GI disease. Symptoms related to GSE are milder than those seen in patients with CD without skin findings, but may include malnutrition, weight loss, abdominal pain, dyspepsia (even mimicking peptic ulcer), and perforation. Deficiency states (folate, iron, B₁₂), neurologic disturbances, bone disease, infertility, chronic fatigue, and premature dental loss may all be seen.

Patients with DH, similarly to those with CD, have a higher incidence of associated autoimmune disorders, including thyroid disorders, atrophic gastritis, type I diabetes, pernicious anemia, Addison disease, vitiligo, and various connective tissue disorders.⁴¹ They are at an increased risk for developing GI lymphoma of T-cell lineage, usually described as enteropathy-associated T-cell lymphomas.¹¹¹ When DH is diagnosed, examinations for possible signs and symptoms of such associations should be considered.¹¹²

The diagnosis of DH is based on clinical, histologic, and IF criteria. DIF of perilesional skin shows granular deposition of IgA and C3 along the BMZ, mostly confined to the tips of the dermal papillae (Figure 22.17). Serum antibodies to tissue transglutaminase are detected using ELISA.

The cornerstone of treatment of DH is the gluten-free diet (GFD) for a lifetime and administration of sulfones, such as dapsone 50–100 mg/daily. In patients who do not tolerate dapsone due to side effects (hemolysis, methemoglobinemia,

agranulocytosis) or glucose-6-phosphate dehydrogenase deficiency, the cutaneous eruption can be alternatively controlled by sulfapyridine 0.5–2.0 g daily (to a maximum dose of 4 g/daily). Strict adherence to a GFD may result in remission of both the skin lesions and the bowel disease. The results of a retrospective study of 487 patients with DH showed a protective role of the GFD against development of lymphoma in DH patients.¹¹³

CONCLUSIONS

Autoimmune blistering diseases are characterized by tissue-bound and circulating autoantibodies to structural components of the skin. The binding of autoantibodies to their target antigens in the skin results in loss of cohesion and formation of intraepidermal or subepidermal blisters. Rupture of blisters leads to painful erosions and significant loss of fluid, electrolytes, and proteins, especially in cases of extensive body surface involvement. Involvement of the oral mucosa, pharynx, and esophagus may lead to inadequate intake of food, liquids, and medications. These changes lead to immunosuppression, which along with the lack of epidermis secondary to erosions predispose patients to life-threatening infections and sepsis. These disorders are important for the morbidity associated with the involvement of skin and mucous membranes especially if left untreated. A combination of routine IF techniques with immunoserologic methods such as ELISA and immunoblot is the rational approach to the diagnosis of patients suspected of having an autoimmune blistering disease.

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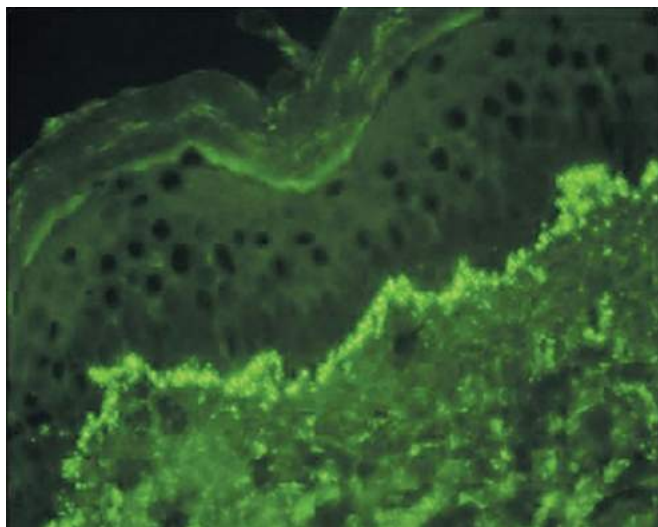


Figure 22.17 Dermatitis herpetiformis: direct IF on perilesional skin showing granular IgA deposits at the dermal-epidermal junction, more intense in the tips of the dermal papillae.

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Emergency management of purpura and vasculitis, including purpura fulminans

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Purpuric lesions are the clinical expression of the passage of erythrocytes from the vascular compartment to the extravascular one, generally following damage related to permeabilization of the walls of small vessels. At times, they are the only clinical feature; at other times, they are a sign of a more complex morbid process and the expression of a serious condition, as in the systemic vasculitides.

The clinical spectra of vasculitides are broad with a variety of conditions ranging from mainly cutaneous involvement with a relatively benign course, such as leukocytoclastic vasculitis, to situations in which the cutaneous involvement is less evident but an integral part of a process that could progress to a critical situation requiring emergency treatment. Acute pulmonary insufficiency or renal blockage, as an expression of a systemic vasculitis, is relatively frequent in intensive care units.^{1,2} Central and peripheral nervous system involvement, cardiac failure, and intestinal ischemia, as complications or first presenting signs of systemic vasculitides, are clinical conditions commonly encountered in current practice.^{3–5} Purpura fulminans (PF), often associated with disseminated intravascular coagulation (DIC), is a dramatic condition that must be identified correctly and differentiated from purpura simplex.⁶ Purpuras and vasculitides are medical emergencies that require rapid diagnosis, identification of the causal factors, and initiation of a treatment, which is often aggressive but must be carried out as early as possible.⁷ Particularly important are some situations occurring in IgA vasculitis (IgAV, Henoch–Schönlein purpura, HSP), granulomatosis with polyangiitis (GPA, Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, Churg–Strauss), polyarteritis nodosa (PAN), microscopic polyangiitis (MPA), Kawasaki disease (KD), and PF (Table 23.1).

Dermatologists may encounter situations involving the evolution or complications of pathologies with initial cutaneous involvement or be called to assist with the diagnosis and management of emergency patients; therefore, knowledge of the disease entities included in the group of purpuras and vasculitides, particularly of the conditions that could progress to emergency situations, must be an integral part of the dermatologist's training. The aim of this chapter is to call attention to purpuras and vasculitides that can present as or evolve into emergency situations and to the procedures for managing these patients.

CLINICAL PRESENTATION AND PATHOGENESIS IgAV

HSP, recently called as IgAV, is an immunoglobulin A (IgA)-mediated leukocytoclastic vasculitis characterized by antiseptic

lesions with perivascular infiltrates, fibrinoid necrosis, and vascular occlusion caused by platelet thrombi. In the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, IgAV replaced the eponym “Henoch–Schönlein purpura” due to the compelling literature, showing that abnormal IgA deposits in vessel walls are the definitive pathophysiologic feature.^{8,9}

The disease is the most prominent vasculitis seen in childhood, sometimes following an upper respiratory tract infection, and various viral and bacterial pathogens are noted as triggers of the disease. It has an acute onset distinguished by cutaneous manifestations on the buttocks and extensor surfaces of the extremities and by general symptoms such as discomfort, headache, fever, polyarthralgia, and abdominal pain. In most cases, IgAV resolves without leaving any negative traces, but in some cases kidney involvement can progress to renal insufficiency.¹⁰

The cutaneous involvement begins with a symmetric macular erythematous eruption on the lower extremity, which rapidly evolves into purpura. Initially, the eruption may be limited to the malleolar skin but usually extends to the dorsal surface of the legs, buttocks, and ulnar side of the upper extremities. Within 12–24 hours, the macules turn into palpable dark red purpuric lesions, sometimes merging into vast ecchymosis-like patches. In children younger than 2 years, the cutaneous involvement may be dominated by marked edema on the scalp, periorbital region, hands, and feet. The intensity of the edema, attributed to the intestinal loss of proteins, is related to the severity of the vasculitis. Palpable purpura occurs in all cases of IgAV and is almost always the first presenting sign, whereas articular involvement and possible renal and abdominal involvement appear later.¹¹ Purpura, arthralgia, and abdominal pain are commonly referred to as the “classic triad” of IgAV. Joint, gastrointestinal, and renal involvement are frequent, but myocarditis, orchitis, alveolar hemorrhage or episcleritis, central or peripheral system involvement may also take place.⁹ Impairment of renal function, bowel perforation, and central nervous system involvement is a rare, but major, morbidity of IgAV.¹²

In the criteria proposed by the European League against Rheumatism (EULAR), Paediatric Rheumatology International Trials Organisation (PRINTO), and Paediatric Rheumatology European Society (PRES) for the classification of childhood vasculitides, a prerequisite for the diagnosis of IgAV is palpable purpura associated with another clinicopathologic features, such as diffuse abdominal pain, tissue deposits of IgA, arthritis or arthralgia, renal involvement shown by hematuria, or proteinuria.¹³ The cutaneous manifestations are crucial for an early preliminary diagnosis, which must then be confirmed.

* Deceased.

Table 23.1 Purpuras and Vasculitides Potentially Evolving into Emergency Situations

Disease	Possible conditions requiring emergency treatment
IgA vasculitis	Abdominal and renal complications
Granulomatosis with polyangiitis	Pulmonary and renal involvement
Eosinophilic granulomatosis with polyangiitis	Hemoptysis and respiratory failure, myocardial infarction, myocarditis, renal failure
Microscopic polyangiitis	Deterioration of renal function and respiratory failure
Kawasaki disease	Cardiac involvement in the acute stage; development of coronary artery aneurysms later in the course
Purpura fulminans	Disseminated intravascular coagulation

GPA

WG is a multisystemic vasculitic disease, recently renamed “granulomatosis with polyangiitis” (GPA). The 2012 revised Chapel Hill criteria⁸ defined GPA as a necrotizing granulomatous inflammation of the upper and lower respiratory tracts, with necrotizing vasculitis of small and medium size vessels. While necrotizing glomerulonephritis is common, it is not essential for the classification. Based on this classification, granulomatous inflammation does not necessarily need to be proven histologically and can be determined by noninvasive studies.¹⁴ Both sexes, usually between 45 and 65 years of age, can be affected, although there are occasional cases of children and people older than 70 years. The etiology is unknown, associated with a significant genetic susceptibility, that contributes to pathogenesis of the disease.^{15,16}

An autoimmune etiology of GPA is suggested by the almost constant presence of granular pattern antineutrophil cytoplasmic antibodies (c-ANCA), the levels of which are correlated with the severity of the disease and are predictive of relapses. The frequent finding of IgA and IgE, the possible association with human leukocyte antigen (HLA) HLA-B8 and HLA-DR2, and the efficacy of immunosuppressive therapy are further elements supporting an autoimmune origin.¹⁷ Protease-3 (PR-3), an enzyme stored in the azurophilic granules of neutrophils and monocytes, seems to be the main target of c-ANCA. Another enzyme, a myeloperoxidase (MPO) contained in the azurophilic granules, could play a role, because it is activated by perinuclear pattern antineutrophil cytoplasmic antibodies (p-ANCA), found in a small number of patients.¹⁸ In vitro studies have shown that ANCA are able to activate leukocyte degranulation and the release of toxic radicals and lysosomal enzymes responsible for a cytokine-mediated inflammatory process.¹⁹ In vivo studies have not provided direct evidence of the responsibility of ANCA in the pathogenesis of GPA.²⁰ The role of an infectious agent has been hypothesized on the basis of the good results of sulfamethoxazole-trimethoprim treatment of early signs of the disease.²¹ Another consideration is nasal carriage of *Staphylococcus aureus*.¹⁴ The histopathologic features seen in recent lesions confirm the hypothesis of an immune-mediated pathogenesis, because they document an involvement of neutrophils and endothelial cells as possible targets and promoters of the inflammation. We know that endothelial damage and neutrophil activation can produce mediators of inflammation that lead to the recruitment of monocytes and T cells able to increase the endothelial damage.

Clinically, there may also be fever and weakness in 50% of the patients. The disease begins with the classic triad of respiratory tract involvement, systemic vasculitis of the small vessels, and focal glomerulonephritis, although the clinical pattern is not always complete. Ear, nose, and throat (ENT) findings are present in 70%–100% of cases, also the most notable manifestation is nasal-sinus involvement, which may be the only sign in the localized forms. The first sign is typically nasal obstruction with hyposmia or anosmia.¹⁴ The other findings are hemorrhage, necrosis, and ulceration that can even lead to destruction of the septal cartilage and deformation of the nasal profile.¹⁴

Lower respiratory tract involvement occurs in approximately 50% of cases, with pulmonary, nodular, and cavity lesions, a frequent cause of hemoptysis. The most common renal involvement is focal segmental necrotizing glomerulonephritis associated with extracapillary proliferation and pauci-immune crescent formation.¹⁴

The joints, eye, and nervous system can be compromised to variable degrees according to the progression of the disease. The peripheral nervous system of roughly one-third of patients is involved, being characterized by mononeuritis multiplex or the less common sensorimotor neuropathy. Central nervous system involvement is less likely to occur (6%–13%) and may be a result of granulomatous deposits.²²

The clinical picture is rarely dominated by cutaneous lesions, the initial frequency of which is relatively low but can rise to more than 50% in the advanced phases of the disease. The first and most typical signs are papulonecrotic lesions located mainly on the elbows, knees, and buttocks, sometimes preceded by an erythematous, edematous, or vesicular inflammatory phase. Subcutaneous nodules and intraoral or genital ulcerative lesions with the appearance of pyoderma gangrenosum and raspberry-red gingivitis can be found at the onset and in the later phases. Purpuric manifestations involving extensive skin areas, associated or not with erythematous and vesicular lesions, are observed more frequently in the late phases of GPA but can sometimes be present at onset and are an important sign for diagnostic purposes.²³

At least two different phenotypes can be distinguished in GPA: localized/limited and systemic/diffuse/severe. The localized forms manifest mainly through ENT involvement, naturally limited to the upper respiratory tract, but recurrent and refractory (known as “grumbling disease”).²⁴ These localized forms appear to predominantly affect young women. The diffuse forms may manifest through renal involvement and/or intraalveolar hemorrhage (IAH), and/or the involvement of at least one vital organ or that of a nonvital organ but in association with constitutional signs (fever, weight loss). Initially, they are typically more serious, but relapse is less common.²⁵

The diagnosis of GPA generally follows histopathologic examination of a tissue fragment taken from the nasal mucosa and is generally based on the demonstration of granulomatosis and vasculitis. Over 90% of patients with GPAs have the appearance of c-ANCA with antiproteinase-3 specificity.¹⁴ The detection of ANCA and the identification of their pattern (i.e., cytoplasmic or perinuclear) are useful diagnostic complements and can contribute to a more complete classification, which naturally requires instrumental and functional examinations of the respiratory apparatus and kidneys.

EGPA

EGPA, formerly known as Churg–Strauss syndrome, is a systemic necrotizing vasculitis that impacts small-to-medium-sized

vessels.⁸ Although EGPA is part of the spectrum of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides, it is differentiated from GPA and microscopic polyangiitis due to severe asthma, plus blood and tissue eosinophilia. Between 30% and 70% of EGPA patients have a positive ANCA.²⁶⁻²⁸

ANCA, circulating antibodies directed against antigenic constituents of the cytoplasm of polymorphonuclear neutrophils, seem to play an important role in the pathogenesis of the disease. *In vitro* studies have shown that various types of antigenic stimuli (such as drugs, allergens, vaccinations, viruses, and bacteria) increase the serum levels of tumor necrosis factor- α (TNF- α) and interleukin-1, with activation of polymorphonuclear neutrophils and transfer of PR-3 from the intracytoplasmic azurophilic granules to the cell membrane. The interaction of PR-3 with circulating ANCA causes the subsequent degranulation of polymorphonuclear neutrophils and tissue damage. Several studies suggest that ANCA are more involved in the vasculitic manifestations, such as glomerulonephritis, whereas the eosinophilic infiltration and the associated cytotoxicity could be responsible for the cardiomyopathy. If confirmed, these results would support an individual stratification in accordance with the clinical pattern.²⁹

The onset of the syndrome is often ambiguous, with the appearance of mainly asthmatic or rhinitic respiratory symptoms that can precede the visceral, neurologic, and cutaneous involvement by some years. Classically, there are three phases: the initial one characterized by allergic rhinitis, nasal polypsis, sinusitis, and asthma; the intermediate one with recurrent episodes of pneumonia and gastroenteritis associated with circulating eosinophilia; and the final one in which respiratory involvement prevails. In the final phase, there may also be digestive apparatus involvement with the appearance of hematic diarrhea, urinary apparatus involvement with hematuria, articular involvement with arthralgia, and heart and peripheral nervous system involvement. The latency between the appearance of the first clinical manifestations and the advanced phase is 3 years on average. Death is generally due to a granulomatous infiltration of the heart or vasculitis of the coronary arteries.³⁰

Cutaneous involvement in EGPA occurs in approximately 70% of cases and is often late and polymorphic, with purpuric maculopapular lesions on the extremities, mainly the acral parts. More rarely, there are cutaneous and subcutaneous nodules on the head and extremities. The cutaneous lesions do not differ from those found in other forms of vasculitis and are characterized by purpuric manifestations, nodules, and polymorphic-like erythematous patches, livedo reticularis, vesicles, aseptic pustules, petechiae, ecchymoses, and urticarial lesions with possible progression to necrosis.^{31,32}

Histologically, EGPA was first described as a pathologic triad made up of eosinophilic infiltration, necrotizing vasculitis, and extravascular granuloma formation.³³ The granuloma presents basophilic or eosinophilic staining, according to the predominance of neutrophils or eosinophils in the infiltrate. The process can involve both small vessels of the dermis and larger vessels of the subcutis, although the finding of vasculitis is not constant. At times, it is possible to observe deposits of C3 and fibrin in the vessel wall.³⁴

PAN

PAN is a multisystemic vasculopathy of medium and small arteries, mainly involving the skin, kidneys, nerves, and

gastrointestinal (GI) tract. Although the disease may involve small arteries, small vessels such as arterioles, capillaries, and venules are typically spared. As a result, glomerulonephritis and pulmonary capillaritis are not part of the PAN spectrum. Antineutrophil cytoplasmic antibodies (ANCAs) are usually negative, so they help to distinguish PAN from other systemic necrotizing vasculitides.³⁵

Men are more likely to be affected by PAN than women, and the disease impacts all ethnic groups. PAN usually occurs between ages 50 and 60.³⁶

The pathogenetic mechanisms leading to the vascular damage are probably heterogeneous and involve the intervention of immune complexes, ANCA, adhesion molecules, cytokines, and antibodies against endothelial cells. The immune complexes are the result of previous infections and act via the activation of complement able to attract neutrophils. ANCA play an important role in inducing endothelial damage but are not always present in PAN. Various adhesion molecules (lymphocyte function-associated antigen 1, intercellular adhesion molecule 1, endothelial cell leukocyte adhesion molecule 1) are able to favor contact between neutrophils and endothelial cells and to initiate the cascade of events leading to vasculitis.

In approximately 10% of subjects with PAN, there is a contemporaneous hepatitis B virus (HBV) infection. In these patients, circulating immune complexes, formed by HBV antigens and relative antibodies, could play an important role in the pathogenesis of the vasculitic lesions.^{37,38} Hepatitis C virus (HCV), along with human immunodeficiency virus (HIV), cytomegalovirus, and parvovirus B19 may also be found.^{35,39}

The disease can develop after a phase characterized by specific symptoms, such as discomfort, fever, weight loss, and muscular and/or articular pain. Cutaneous involvement is frequent with purpuric lesions, livedo reticularis, nodules, ulcers, and gangrene. The most frequent cutaneous signs are painful nodules of variable size and number, located mainly on the legs. The nodules are usually the first cutaneous sign; they appear after a more or less long benign course and develop with multiple flares, leaving a pigmented or livedoid residue with a characteristic reticular pattern. Livedo reticularis is more evident in some areas, such as the legs, feet, buttocks, and shoulder blades, and can persist as the only evidence of vascular damage.⁴⁰

The rupture of inflamed arteries may produce tissue ischemia or hemorrhage in various organs and systems. Mononeuritis multiplex is the primary neurologic manifestation, which presents with wrist or foot drop, although symmetrical polyneuropathy is also known to occur. The gastrointestinal tract and kidneys are often involved. Manifestations in the gastrointestinal tract are among the most severe indications of PAN, and one-third of cases show that this disease manifests as an acute surgical abdomen.⁴¹ Renal involvement in PAN comprises tissue infarction or hematoma, usually produced from the rupture of renal microaneurysms. Glomerulonephritis is not caused by PAN, and hypertension secondary to intrarenal artery involvement is often observed.³⁶

In addition to the systemic idiopathic form, the PAN spectrum includes "cutaneous PAN" and "hepatitis B virus (HBV)-associated PAN." These clinical forms are critical, because they hold specific therapeutic implications.³⁶

MPA

The 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides defines MPA as

necrotizing vasculitis, with fewer no immune deposits, primarily affecting small vessels such as capillaries, venules, or arterioles, frequently associated with glomerulonephritis and pulmonary involvement.⁸ Considered the microscopic form of PAN, it acquired clinical autonomy in 1994 after the consensus conference aimed at redefining the classification of small-vessel vasculitides.⁴² Involvement of the small vessels, including arterioles, capillaries, and venules, is absent in PAN but is typical of MPA. In pathogenetic terms, MPA, along with GPA and EGPA, belongs to the group of small-vessel vasculitides linked to the role of ANCA. Anti-MPO p-ANCA antibodies, present in MPA and absent in PAN, help to differentiate the two disease entities.⁴³ The absence of granulomas and the lack of upper respiratory tract involvement help to distinguish MPA from GPA, although the distinction is not always easy.⁴⁴

MPA generally has a rapid and progressive course, and a timely diagnosis can be important for effective treatment. MPA primarily involves the kidneys and the lungs. The finding of cutaneous signs may be useful for the purposes of the histologic examination. They present as erythematous or purpuric macules, mainly located on the extremities and are observed in more than 50% of cases.⁴⁵

Renal involvement manifests as microscopic hematuria and rapidly progressive glomerulonephritis. Although lung involvement occurs less frequently, it is manifested by dyspnea, cough, and hemoptysis. Pulmonary hemorrhage is a severe condition with a bad prognosis particularly for patients with rapidly progressive glomerulonephritis. Malaise, weight loss, and fever, arthralgia/myalgia, skin involvement such as purpura, and, particularly, involvement of peripheral nerves (mononeuritis multiplex occurring in around 50% of patients) are commonly observed.⁴⁶ The cutaneous histopathology of MPA is characterized by a necrotizing vasculitis with a moderate neutrophilic infiltrate affecting the papillary and middle dermis and the subcutaneous tissue. ANCA in MPA are predominantly directed against myeloperoxidase (MPO-ANCA) but may, in a limited number of patients, be directed against proteinase 3 (PR3-ANCA); however, not all patients have ANCA.^{35,46}

KD

KD, or mucocutaneous lymph node syndrome, is a vasculitic syndrome of unknown origin described in 1967, characterized by an eruption associated with fever of relatively brief duration. Initially thought to be a benign self-resolving process, it was later related to a series of deaths from myocardial infarction due to thrombotic occlusion of aneurismatic coronary arteries. Exceptional in adolescents and adults, KD is typically a childhood disease typically presented at 6 months to 5 years of age with a higher incidence in Asian populations, particularly in Japan and China.⁴⁷ An estimated 90% of patients show mucocutaneous manifestations, making early diagnosis and intervention critical for preventing cardiovascular morbidity and mortality.⁴⁸

The etiology of KD is unknown, although the idea of an infectious origin is attractive. This origin is suggested by the self-resolving course, lack of relapses, fever, exanthema, and adenopathy, all typical of an infectious disease. Epstein-Barr virus, *Mycoplasma pneumoniae*, varicella zoster virus, and human adenoviruses are unconfirmed pathogens.^{48–50} Direct attempts to isolate an infectious agent have proven negative. It is possible that KD is the result of an immune response

induced by different microbial agents. This hypothesis is supported by the frequent isolation of infectious microorganisms in individual cases and the similarities to other syndromes caused by multiple agents, such as aseptic meningitis.⁵¹

The inflammatory infiltrate found in KD, characteristic of a vasculitis, can involve blood vessels throughout the organism. In autopsies, aneurysms have been found in arteries in many regions (e.g., the celiac, mesenteric, femoral, iliac, and renal arteries).⁵²

The diagnostic criterion is based on fever lasting at least 5 days accompanied by about four of five mucocutaneous criteria. These criteria are alterations of the extremities, characterized in the acute phase by palmo-plantar edema and in the subacute phase by desquamation of the fingertips, hands, and feet. Other typical signs are polymorphic exanthema, bilateral hyperemic conjunctivitis without secretion, redness of the lips and oral cavity, fissuring of the lips, strawberry tongue, and hyperemia of the pharynx and oral cavity. A usually unilateral laterocervical lymphadenopathy is also frequently observed.⁵³

Cardiovascular symptoms may be evident as early as the acute phase of KD, and they are the main cause of long-term morbidity and mortality. In this phase, the pericardium, myocardium, endocardium, valves, and coronary arteries can be involved. Cardiac function shows anomalies, such as tachycardia and myocardial contractile deficit, a cause of insufficiency and shock.⁵⁴ Coronary artery aneurysms develop in 15%–25% of untreated persons and can lead to myocardial infarction, sudden death, or ischemic cardiac disease.^{55,56} Various point systems are available to identify children at high risk of coronary arteriopathy.⁵⁷

Arthritis and arthralgia prevalence ranges between 7.5% and 30%. Arthritis may be polyarticular or oligoarticular, mainly involving the larger joints; it is usually painful. Abdominal pain, diarrhea, and vomiting, are commonly experienced in up to one-third of patients.

PF

PF is a hematologic emergency with skin necrosis and disseminated intravascular coagulation. This may quickly progress to multiorgan failure due to thrombotic occlusion of small and medium-sized blood vessels.⁵⁸

PF, a disease generally associated with sepsis, is found most frequently in children. The clinical pattern is often dominated by shock with hypotension and hypovolemia, clinically distinguished by a weak and frequent pulse, anxiety, pallor, cold sweating, and cyanotic lips. The cutaneous lesions consist of purpuric patches that rapidly evolve into peripheral hemorrhagic necrosis, sometimes preceded by bulla formation.⁵⁸ PF is almost always associated with or progresses to DIC, an expression of thrombocytopenia with increased production of thrombin and fibrinolysis (Figures 23.1 and 23.2). PF may cause multiorgan failure or severe large vessel venous thrombosis and result in high initial mortality and long-term morbidity in survivors.⁵⁸

The lesions in PF are generally considered the result of a Schwartzman-like reaction. The Schwartzman phenomenon occurs when a dose of endotoxin is intravenously injected into animals previously inoculated subcutaneously with a small dose of the same endotoxin. The reaction occurs within a few hours at the site of the first inoculation and is characterized by an inflammatory event that rapidly progresses to necrosis. The Schwartzman phenomenon cannot be explained by an



Figure 23.1 PF and DIC in a 71-year-old man suffering from leg ulcers and diabetes. Note the multiple hemorrhagic bullae.



Figure 23.2 Cellulitis with signs simulating PF in a 56-year-old woman. The clinical presentation was dominated by the appearance of purpuric patches, hemorrhagic bullae, and fever.

immune mechanism and is probably due to a toxic effect. In PF (at least in the forms associated with sepsis), the vascular lesions are considered the result of a necrotizing inflammatory process caused by infectious agents. Meningococcus is the most frequent cause of PF, but other infectious agents have been recorded, such as *Pneumococcus*, varicella zoster virus, and *Staphylococcus*.^{59–61} A malignant tumor, a possible triggering factor in PF, has been found in a significant number of cases.⁶² PF is caused by severe heritable protein C (PC) deficiency.⁵⁸

This progression in the clinical appearance of PF correlates with the histologic appearance of occlusion of small dermal vessels with microthrombi, causing capillary dilation and congestion with red cells in early PF. In later stage lesions, there is irreversible endothelial ischaemic injury with extravasation of blood cells into the dermis and gangrenous necrosis sometimes with secondary infection.⁶³ This feature differentiates PF from other vasculitides, such as IgAV, characterized by an accentuated inflammatory component.⁶⁴

PF is associated with marked hematic alterations, particularly low concentrations of fibrinogen, coagulation factors,

and platelets, due to consumption of platelets and extended prothrombin and partial thromboplastin times. Fibrinogen-degradation products tend to increase, and the concentrations of proteins C and S and antithrombin III (AT III) tend to decrease. DIC often develops under these conditions; it is the consequence of anomalous thrombin activation leading to the conversion of fibrinogen to fibrin, as well as of the activation and consumption of platelets. These coagulation alterations are believed to be related to systemic anomalies, particularly activation of protein C, which are congenital or induced by pathologic conditions.⁶⁵

MANAGEMENT AND TREATMENT

The treatment of patients affected by purpuras and vasculitides, in critical or emergency conditions, is based on general and case-specific measures. Useful general procedures are those aimed at improving the hemodynamic and hydroelectrolytic imbalance and correcting eventual coagulation anomalies, which could require specific drugs in addition to substantial plasma and/or whole-blood infusions.

Systemic vasculitides, associated with circulating ANCA, are characterized by frequent renal parenchyma involvement, represented by a necrotizing glomerulonephritis, which translates into acute renal insufficiency. The presence in the blood of autoantibodies with an important role in the pathogenesis of the lesions has prompted the use of plasmapheresis, on the assumption that rapid removal of the autoantibodies and, at the same time, coagulation factors and mediators of inflammation could strongly affect the progression of the disease (Table 23.2).^{66,67}

Corticosteroids are the most important category of immunosuppressor drugs used in the treatment of systemic vasculitides. They can be useful in all forms of vasculitides but are the first-line agents in several forms, such as GPA, EGPA, and PAN. Corticosteroids can be used alone in the less severe forms but are usually combined with cyclophosphamide in the severe forms. Other immunosuppressors, such as azathioprine and methotrexate, are used as maintenance therapy in the remission phases of the disease.⁶⁸

Table 23.2 Drugs and Procedures Used in the Treatment of Emergencies Related to Purpuras and Vasculitides	
Drugs and procedures	Indications
Plasmapheresis	ANCA-associated systemic vasculitides
Corticosteroids	All vasculitides; first-line treatment in GPA, EGPA, PAN
Cyclophosphamide	Associated with corticosteroids in GPA, EGPA, PAN
Azathioprine and methotrexate	Used as maintenance therapy in patients with GPA, EGPA, PAN
Intravenous immunoglobulins	First-line treatment in Kawasaki disease; potential alternative treatment for ANCA-associated systemic vasculitides
Infliximab	Able to induce clinical remission in acute or active ANCA-associated vasculitides
Rituximab	Active in refractory or relapsed ANCA-associated GPA

Notes: ANCA, antineutrophil cytoplasmic antibodies; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; PAN, polyarteritis nodosa.

The appearance of IV immunoglobulins (IVIG) has further expanded the therapeutic arsenal for systemic vasculitides. At high doses, IVIG can interfere with the immune system at various levels, being indicated in various pathologies based on inflammation-immune mechanisms. IVIG have proven particularly useful for KD, but their use (alone or associated with corticosteroids or other immunosuppressor) has also proven successful in the ANCA-associated vasculitides.⁶⁹

Newer prospects in the treatment of systemic vasculitides have been provided by the introduction of the biologics, particularly infliximab, etanercept, and rituximab. In association with conventional therapy, infliximab, an anti-TNF chimeric monoclonal antibody, has been able to induce clinical remission in various systemic vasculitides,⁷⁰ whereas the efficacy of etanercept has been modest. Rituximab, a genetically chimeric murine-human CD20 antigen expressed on the surface of B lymphocytes, is more promising, as it has proven effective against refractory or relapsed ANCA-associated GPA.⁷¹

IgAV

The management and therapy of IgAV patients must take into account various factors such as age, possible renal involvement, and the presence of complications such as nervous system involvement. IgAV is generally a benign disease with a good prognosis, characterized in more than 80% of patients by a single episode lasting a few weeks, with relapses in 10%–20% of cases and chronic forms, particularly renal insufficiency, in 5% of cases. For this reason, the usefulness of always adopting a systemic therapy has been placed in doubt, particularly treatment with steroids, because placebo-controlled prospective studies have shown their limited efficacy.⁷²

Benign manifestations, such as nonnecrotic purpura or arthralgias, are typically managed by symptomatic measures (resting, analgesia, compression stockings). Angiotensin-converting enzyme inhibitors are required in the case of kidney involvement with mild to moderate proteinuria; colchicine and dapsone may improve symptoms and patient quality of life for those with chronic IgAV with purpura; Montelukast, a leukotriene receptor antagonist, reduces the clinical manifestations of IgAV including purpura, abdominal pain, stool occult blood, arthritis, proteinuria, and hematuria.⁹

Corticosteroids are effective for arthralgias and abdominal pain, but they are ineffective for skin purpura. There is much controversy surrounding the benefits of corticosteroids to treat renal involvement and prevent evolution to end-stage renal disease.⁹ Prednisone, at 1 mg/kg/day for 2 weeks followed by a lower dose for another 2 weeks, has been shown to improve the GI and articular involvement and to reduce the severity of renal involvement. According to the 2012 KDIGO guidelines, patients with IgA nephropathy should be treated for persistent proteinuria >1 g/day despite 3–6 months of optimized supportive care (including renin-angiotensin-aldosterone system inhibition and blood pressure control), and eGFR >50 mL/min, with 6-month course of pulse methylprednisolone and low dose prednisone therapy.⁷³

Other immunosuppressors (e.g., azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil) can be combined with steroids, although their use is controversial in view of the low efficacy recorded in clinical trials.⁷⁴ Cyclosporin A has been demonstrated a very effective and safe treatment in patients with nephrotic-range proteinuria. In those with rapidly progressive glomerulonephritis, multiple-drug therapies

include methylprednisolone followed by prednisone, methylprednisolone combined with urokinase pulse therapy with or without mizoribine, and corticosteroid with azathioprine, mizoribine, or cyclophosphamide, have been shown to be useful; however, not enough evidence has shown that immunosuppression drugs or multiple drugs are more effective. The results about mycophenolate mofetil are promising but still insufficient to understand the real efficacy. A therapeutic monoclonal antibody against the surface antigen CD20 expressed by B cells, rituximab, is thought to reduce circulating IgA and could be an attractive option for patients with refractory HSP. Some adjuvant therapies such as immunoglobulin, anticoagulants, antiplatelet drugs, and vitamins have also been used but currently are not recommended.^{74–76} Plasmapheresis deserves separate mention, because it has proven effective in delaying the progression of renal damage.⁷⁶

GPA

GPA is a severe condition, with a high fatal outcome when not treated. Renal involvement in GPA determines both the functional renal prognosis and the life-threatening potential of the disease. Relapses often occur during GPA. In the first year following the diagnosis of GPA, primary causes of mortality may be infection (32%) and kidney failure (18%). One-quarter of patients relapse within 2 years of diagnosis, and over half relapse within 5 years. There is a sevenfold relative risk of relapse in chronic nasal carriers of *S. aureus*.⁷⁷

The use of conventional immunosuppressors has led to significant improvement of the course and prognosis of GPA, although there are still serious limitations due to possible cytotoxic side effects and frequent relapses after the suspension of treatment. Many doubts remain about the use of the biologics, whereas there is great hope concerning the possible development of drugs that will interfere with specific targets with an important role in maintaining the autoimmune response (e.g., ANCA).^{78,79}

There are two phases of treatment. The first phase, known as the induction phase, aims to quickly put the disease into remission, and lasts about 3–6 months based on clinical response. The second phase, known as the maintenance phase, consolidates the remission and limits the risk of relapse; it lasts for 12–24 months.¹⁴

The standard treatment of GPA involves the combination of cyclophosphamide and corticosteroids until remission and then maintenance therapy with azathioprine or methotrexate.⁸⁰ When selecting the initial treatment regimen for remission induction of active disease, clinicians must determine whether to administer corticosteroids as an intravenous (IV) pulse (typically 500–1000 mg daily for 3 days), the starting dosage of corticosteroids to use, and how to reduce oral corticosteroids, while maintaining a balance between efficacy and toxicity.⁸¹

Replacing cyclophosphamide with methotrexate after remission is achieved may be advantageous in view of its low toxicity, and it could be used as the first-line agent in association with corticosteroids.⁸² All the previously mentioned drugs induce immunosuppression with the consequent risk of opportunistic infection, above all *Pneumocystis jiroveci* pneumonia, although this can be prevented by sulfamethoxazole-trimethoprim treatment, especially during remission. This drug has also been used satisfactorily to reduce relapses, above all in patients with limited, not very aggressive forms.

GPA has also been the subject of trials to assess the efficacy of biological drugs, especially by means of anti-TNF- α agents, likely involved in the pathogenesis of GPA. Etanercept, a soluble TNF receptor fusion protein, is not very effective, inducing long-lasting remissions in only a minority of the treated patients⁸³; moreover an association between therapeutic inhibition of tumor necrosis factor (TNF) and solid malignancies was observed during the Wegener's Granulomatosis Etanercept Trial (WGET).⁸⁴ Infliximab, a chimeric monoclonal antibody against TNF, seems to merit further investigation⁸³; however, anti-TNF- α therapy does not play a regular role in GPA treatment.

Rituximab, a chimeric monoclonal antibody against CD20, is more interesting because it causes depletion of B cells in the blood within 6–12 months. By this mechanism, rituximab seems to recreate the tolerance to ANCA antigens, at least in some GPA patients, and is effective in GPA maintenance therapy.⁸⁵ A single course of rituximab has similar safety and efficacy to continuous conventional immunosuppressive therapy in remission induction and maintenance out to 18 months. Additionally, rituximab has proven effective for treatment of severe disease flares despite previous treatment history.^{80,86}

GPA can also be treated with other drugs, including leflunomide, mycophenolate mofetil, IVIG, deoxyspergualin, and plasma exchange. Leflunomide inhibits *de novo* synthesis of pyrimidine, necessary for the function of activated T lymphocytes. Its use in GPA can control relapses in a high number of subjects.⁸⁷ Mycophenolate mofetil is an inhibitor of inosine monophosphate dehydrogenase, an essential enzyme for purine synthesis and thus for the proliferation and function of lymphocytes. Its use in the maintenance of remission in subjects treated with corticosteroids and cyclophosphamide has not proven very effective, and it requires further evaluation.⁸⁸ IVIG is a reduction in disease activity, but this difference was not sustained after 3 months.^{69,80} Gusperimus (15-deoxyspergualin) is a synthetic molecule with potent immunosuppressive effects whose mechanism of action is poorly understood but believed to involve modulation of B cells, T cells, and antigen-presenting cells. Two new studies have demonstrated safety and efficacy of gusperimus in patients with refractory GPA.^{80,89} GPA was also treated with alemtuzumab and mizoribine.^{90,91}

EGPA

Overall, EGPA is considered a milder systemic vasculitis with lower mortality compared to other types of vasculitis. It has a remission rate similar to GPA but higher than MPA³³; however, the mortality rate of GPA similar to that of untreated GPA may approach 50% at 3 months, if left untreated.⁹²

The French Vasculitis Study Group has identified five prognostic factors, together called the five-factor score (FFS), in patients with necrotizing vasculitis including GPA: elevated serum creatinine levels (>1.58 mg/dL), proteinuria (>1 g per day), gastrointestinal tract involvement, cardiomyopathy, and central nervous system involvement.⁹²

Corticosteroids are the first-line agents in the treatment of EGPA. They can be used according to the standard procedures, but some authors suggest IV methylprednisolone pulses, especially in emergency situations. The response is usually dramatic; the eosinophilia is normalized, the asthma regresses, and the muscle enzyme levels return to normal. Once a clinical response is determined, typically within a few weeks, steroids

can be gradually tapered to a minimal dose able to control the disease.³³

If the corticosteroids are not sufficient to control the disease, it may be necessary to combine cyclophosphamide (the use of which is always advisable) and steroids in life-threatening cases. Methotrexate could also be helpful to control EGPA and can be associated with steroids.⁹³

In severe cases, particularly when steroids and cyclophosphamide do not induce remission, anti-TNF agents such as infliximab and etanercept can be used, although they could increase the risk of infections. Prophylactic treatment with sulfamethoxazole-trimethoprim may be appropriate. An alternative could be the use of recombinant interferon- α (IFN- α).⁹⁴ There are encouraging results with rituximab, but the data must be confirmed by larger trials.^{95,96} IVIG could be a valid alternative in patients unresponsive to conventional treatment, especially those presenting with cardiomyopathy and neuropathy. The mechanism of action of this therapy is still unclear and requires further investigation, but this does not diminish the practical efficacy of the treatment.⁹⁷

Mepolizumab, a humanized monoclonal antibody against IL-5, has been used in a study of seven patients with steroid-dependent EGPA, both safely and being well-tolerated. It greatly lowered eosinophil counts and allowed patients to drastically decrease the dose of corticosteroids. All patients relapsed after the mepolizumab was discontinued.⁹⁸ Omalizumab has also been unsuccessfully used in an EGPA patient with residual asthma after the remission of the vasculitic phase.⁹⁹ That EGPA may also respond to imatinib as well suggests that eosinophilia in EGPA and HES may share pathophysiologic mechanisms.¹⁰⁰

PAN

PAN prognosis is dependent on the organs involved: first, the systemic forms must be distinguished from the limited forms. The treatment of PAN depends on the severity of the clinical features, quantified by the degree of involvement of the affected organs. In particular, it is necessary to assess the extent of proteinuria and creatininemia, the severity of eventual cardiomyopathy and GI signs, and the nervous system involvement. In general, corticosteroids associated with cyclophosphamide represent the standard treatment of PAN, whereas antiviral agents and plasmapheresis are necessary in HBV-related cases.^{101,102}

In patients with a relatively benign prognosis, corticosteroids alone may be sufficient. First-line corticosteroid therapy can achieve and maintain remission in about 50% of patients with mild PAN. It must be administered until regression of the symptoms, generally after approximately 1 month. The dose can then be tapered to a level able to control the disease, after which the minimal dose must be maintained for 9–12 months. If tapering is unsuccessful (prednisone <20 mg daily) and if remission cannot be reached, or if adverse effects of continued corticosteroid use are unacceptable in patients with mild PAN, methotrexate, azathioprine, or mycophenolate mofetil can be added.^{35,103}

Cyclophosphamide is generally associated when the disease is refractory to treatment with steroids alone, during relapses, and generally in all severe cases. Pulsed IV administration is the most common procedure, but oral administration can be used when it is unsuccessful. The association of cyclophosphamide with steroids for more than 1 year should be avoided. Cyclophosphamide use is recommended to induce

remission, and a safer immunosuppressive agent, such as azathioprine or methotrexate, is advised to maintain remission.¹⁰⁴ Anti-TNF agents have been examined as treatments for PAN in several case reports; however, the evidence is inconclusive.

In HBV-related cases, plasmapheresis is considered the treatment of choice, because it can remove the viral components, including circulating immune complexes. Antiviral agents, such as IFN- α 2b and lamivudine, are obviously important in such cases, possibly in combination. Naturally, corticosteroids are always indicated in PAN.^{105,106} On exceptional occasions, HBV-related PAN may show a fulminant onset, requiring treatment with prednisone combined with pulsed IV cyclophosphamide and lamivudine.¹⁰⁷

MPA

As in other forms of vasculitis, the initial treatment of MPA consists of the induction of remission with prednisone and a cytotoxic agent, such as cyclophosphamide. The initial dose of prednisone is 1 mg/kg/day for 1 month or at least until significant improvement is observed; it is preceded by IV methylprednisolone in more severe cases. This dose is followed by a weekly decrease to the maintenance dose, which can be continued for long periods, possibly on alternate days. IV pulse cyclophosphamide (15 mg/kg at 2 week intervals for the first three doses and every 3 weeks thereafter) appears to be effective as an oral cyclophosphamide (2 mg/kg daily), but seems less toxic, particularly in relation to infections associated with neutropenia, which occur more often during oral cyclophosphamide therapy. Induction of remission usually takes 2–6 months.¹⁰⁸ The initial cyclophosphamide dose is 1.5–2 mg/kg/day, but higher doses may be required (possibly IV) in emergency situations (e.g., in capillaritis with pulmonary hemorrhage).¹⁰⁹ After remission, it is necessary to establish a maintenance regimen, continuing the prednisone and replacing the cyclophosphamide with azathioprine or methotrexate, both at relatively low doses. Alternative drugs to be combined with prednisone in the maintenance phase are methotrexate, cyclosporine, and mycophenolate mofetil.¹¹⁰ *Pneumocystis carinii* and *Pneumocystis jirovecii* infections are prevented by sulfamethoxazole-trimethoprim administered 3 times a week. Plasmapheresis has proven to be beneficial in treating pulmonary hemorrhage and severe kidney disease.¹¹¹ Rituximab may be a viable alternative to cyclophosphamide for patients with higher levels of disease activity, who may not respond well to antimetabolite therapies.³³

KD

The treatment of acute KD is aimed at reducing inflammation in the walls of the coronary arteries and preventing thrombosis, whereas long-term therapy in individuals with coronary aneurysms is aimed at preventing ischemia and myocardial infarction. The acute phase procedures, often carried out in emergency conditions, are based on the earliest possible administration of aspirin and IVIG.¹¹² Coronary artery complications are significantly reduced when treatment is administered within 10 days of symptom onset.¹¹³

Although aspirin is an important antiinflammatory and has antiplatelet aggregation activity, its use alone does not seem to reduce the frequency of coronary alterations. During the acute phase of KD, it is administered at high-dose aspirin (80–100 mg/kg daily divided in four doses) in association with IVIG (2 g/kg in an 8–12 h infusion), which potentiates the

antiinflammatory effect. Aspirin is administered at high doses until fever subsides, generally after 2–3 days, and it is then used at 3–5 mg/kg/day for antiplatelet aggregation until the patient is free of the risk of coronary alterations.¹¹⁴ The mechanism of action of IVIG is still unknown, but administration leads to rapid lowering of the fever and resolution of the clinical signs of KD in most patients. The prevalence of coronary disease drops from 20% to 25% in children treated with aspirin alone to 2%–4% in those treated with IVIG and aspirin in the first 10 days of the disease. IVIG treatment is also indicated in patients diagnosed after the 10th day of the disease if the fever persists, because the antiinflammatory effect could be helpful.¹¹⁵ Occasionally, some patients may not respond to the initial IVIG infusion or show only a partial response. These subjects are usually treated with an additional IVIG infusion, but its efficacy must still be demonstrated.¹¹⁶ About 10%–20% of patients are IVIG-resistant. Risk factors for poor response that can demand more aggressive initial treatment include male sex, age <12 months, delayed initiation of treatment (beyond day 10 after symptom onset), and abnormal laboratory values, such as elevated levels of aspartate aminotransferase, CRP, total bilirubin, and lactate dehydrogenase, increased numbers of neutrophils and bands, and low platelets, albumin, cholesterol, hemoglobin, and sodium levels. When clinical signs have persisted for 36 hours after IVIG infusion and resistance is determined to have occurred, a second 2 g/kg dose of IVIG may be used. After continued resistance to IVIG, a 3-day course of 30 mg/kg/day IV pulse methylprednisolone is often provided.^{113,117,118}

The use of corticosteroids in acute KD remains controversial and still under investigation. According to recent studies, IV administration of methylprednisolone as an adjuvant of conventional therapy with IVIG and aspirin seems to improve the prognosis⁸⁵; however, steroids should not be administered as monotherapy.¹¹³

Another drug used in the acute phase of KD is pentoxifylline, which is well tolerated, practically without toxicity, and perhaps able to further reduce the risk of coronary aneurysms.^{118,119}

Other drugs have been used along with corticosteroids in patients unresponsive to conventional treatment, including cytotoxic agents such as cyclophosphamide and anti-TNF- α monoclonal antibodies (infliximab, etanercept), calcineurin inhibitors, methotrexate, plasma exchange, rituximab, statins, and anakinra.^{113,119,120} Among these, infliximab is particularly promising, but its use requires additional evaluation.¹²¹ Cyclosporine could represent an alternative option in the treatment of refractory forms of KD also given that T cells, the activity of which is inhibited by cyclosporine, are implicated in the pathogenesis of KD; however, the efficacy and safety are still unclear.¹²²

PF

PF is a hematologic emergency requiring immediate intervention due to the rapidly progressive nature of the multiorgan thrombotic injury and due to the frequent association with severe sepsis.⁵⁸ Management of DIC with PF should be based on clinical and associated laboratory findings. PF patients must be treated in an intensive care unit, where appropriate procedures to deal with shock can be carried out. Such procedures, particularly treatment of hypovolemia by infusions of plasma and physiological solution, correction of the acid-base

imbalance, and assisted ventilation, combined with appropriate antimicrobial therapy, have considerably reduced the mortality due to PF. The platelet count should be maintained at $>50,000 \times 10^9/L$ and the fibrinogen level $>1 \text{ g/L}$.¹²³ If the etiology is secondary to severe infection, appropriate IV antimicrobials should be administered.¹²⁴

The efficacy of the treatment to prevent or limit the possible necrotic evolution of acral lesions largely depends on the extent of treatment. The role of dermatologists can be decisive, because they can identify PF and its possible infectious origin on the basis of the first presenting signs. The problem is to distinguish PF from a vasculitis with cutaneous involvement, and this is not always easy to do. Acral involvement, hemorrhagic bullae, a tendency to necrosis, and hypovolemic shock are all suggestive of PF.¹²⁴ Some laboratory tests can be helpful for diagnostic and therapeutic purposes. The blood levels of prothrombin fragments 1 and 2, the D-dimer test, the AT III level, fibrin- and fibrinogen-degradation products, the platelet count, the prothrombin time, and the levels of other coagulation factors can all provide useful indications.¹²⁵

The availability of tests to investigate more thoroughly the coagulation system has led to the isolation and synthesis of new drugs that affect the coagulation process at various levels. These drugs have been added to the traditional therapeutic arsenal and deserve a brief discussion regarding PF treatment (Table 23.3).

Although one of the oldest anticoagulant drugs, heparin can still play a role in the treatment of PF.¹²⁶ It must be administered as early as possible, even though there are some reservations, because it can cause thrombocytopenia and bleeding and there are no validated dosage schedules to use in all cases. Administration as a bolus followed by slow infusion seems to be the most reliable procedure,¹²⁷ but there are reports of relapses due to too early suspension.¹²⁸ The introduction of low molecular weight heparins is interesting in this regard, but further investigation is required.¹²⁹ Anticoagulation therapy should be initiated with administration of protein C replacement therapy and is an effective

long-term secondary prophylaxis. Initial anticoagulation consists of either unfractionated heparin or low molecular weight heparin. Initiation of warfarin therapy should overlap and start only after several days of anticoagulation with unfractionated heparin/low molecular weight heparin to avoid warfarin-induced skin necrosis and other thrombotic complications.¹²¹

Protein C, an important physiologic anticoagulant factor, is a vitamin K-dependent protease activated by thrombin. Its activated form, along with protein S (which acts as a cofactor), degrades factor Va to factor VIIIa. Its blood level is a useful reference to determine the quantity and timing of administration.¹³⁰ The clinical course is the most important parameter for the establishment of when protein C infusion will be useful and if it can be suspended. Protein C is the first-line agent in cases of neonatal PF associated with homozygote protein C deficiency. It is administered by continuous or intermittent IV infusion until normalization and stabilization of the coagulation parameters.^{131,132}

AT III is a glycoprotein produced by the liver with a powerful inhibitory effect on the cascade of reactions involved in coagulation. Although its name indicates activity against thrombin, it interferes with virtually all the enzymes of coagulation and is particularly active when administered with heparin, with which it forms an anticoagulation complex. It is indicated for the prevention and treatment of thromboembolic processes due to AT III deficiency, of which two forms are known: those due to an absolute lack of the factor (type I) and those due to an inadequately functioning AT III (type II).¹³¹

Absolute or functional AT III deficiencies, such as those occurring during a surgical intervention, pregnancy, childbirth, sepsis, polytrauma, and/or other pathologic conditions associated with acute consumption coagulopathy and which can lead to DIC, are elective conditions for the use of AT III, although the efficacy of this treatment has recently been placed in serious doubt.¹³³ AT III can be diminished during PF, and the restoration of normal levels by infusion could help to improve the clinical course.¹³⁴

Plasminogen activators, essential to convert plasminogen to plasmin and to initiate fibrinolysis, include urokinase, streptokinase, and various substances of tissue and vascular origin, particularly tissue plasminogen activator (t-PA), a human enzyme now obtained with the recombinant DNA technique (rt-PA). The rt-PA, currently used in the treatment of myocardial infarction and ischemic stroke, has been applied successfully in the treatment of peripheral thromboses caused by physical agents¹³⁵ and in the treatment of PF.¹³⁶ The rt-PA is able to activate fibrinolysis without unpleasant hemodynamic consequences. It is administered by infusion at 0.25–0.5 mg/kg/h, and treatment can be prolonged if necessary.¹³⁷ The possible risk of bleeding has raised some doubts about the use of rt-PA in PF, and it has been suggested that it be adopted only in forms unresponsive to conventional treatment.¹³⁸

Epoprostenol is generally used to inhibit platelet aggregation during renal dialysis, especially when there is a high risk of hemorrhagic problems following heparin use. It is also used to treat primary pulmonary hypertension refractory to other treatments, generally together with other anticoagulants. Because its half-life is only approximately 3 minutes, it must be administered by continuous IV infusion. As a potent vasodilator, its side effects include hot flashes, headache, and hypotension. In PF from sepsis, it has been used in children

Table 23.3 Anticoagulant Substances Used in the Treatment of PF

Drugs	Indications
Heparin	Mainly as a bolus followed by an infusion; low molecular weight heparins in the prophylaxis of relapse
Protein C	First line in PF due to protein C deficiency; adjuvant hemostatic support in PF-associated meningococcemia
Antithrombin III	Possible lowering in PF; replacement may normalize levels and reverse disseminated intravascular coagulation
Tissue plasminogen activator	Used for PF unresponsive to conventional treatment
Epoprostenol	Used to treat PF from sepsis in infants and neonates
Dextran	Used in PF patients, who fail to respond to plasma and heparin therapy

Note: PF, purpura fulminans.

and neonates at 5–20 ng/kg/min without significant collateral effects.^{139,140}

Dextrans are glucose polymers of variable molecular weight used as plasma substitutes and as antithrombotics, because they are able to reduce platelet aggregation. The rheologic effect produced by these molecules is due to their ability to adhere to the endothelial surface (reducing the reactivity between the cell and vessel surfaces), to hemodilution, to reduction of cell aggregation, and to increased platelet rigidity with consequent reduced adhesive ability and aggregation. These activities are translated into improved flow in the microcirculation and increased oxygen transport. Dextran with a molecular weight of 40 has been used in PF as an adjuvant of other treatments, particularly heparin therapy.¹⁴¹

In meningococcal sepsis, the most frequent event (especially in children), the first-line antibiotic is penicillin; however, in cases in which the nature of the sepsis is unclear, a third-generation cephalosporin, such as cefotaxime, can be used from the beginning. Subsequent strategies are aimed at correcting and restoring the altered coagulation mechanisms. In this context, the use of the drugs reported in Table 23.3 must be weighed and based on the clinical and laboratory findings in the individual cases.

A surgical approach is crucial when treating PF. High incidences of compartment syndrome occur in PF. Anticipation of an emergent fasciotomy should remain high. Compartment syndrome signs include tense, painful compartments, compartment pressures >30 mm Hg, inexplicably high creatine levels, and absent peripheral pulses for more than 4 hours. Fasciotomy compartment release within 6 hours of ischemia is ideal. When amputation is necessary, a balance between a more distal versus proximal amputation should be made.¹⁴²

CONCLUSIONS

Systemic vasculitides can frequently evolve into emergency conditions and sometimes present a critical situation from their onset. The latter occurs most frequently in PF, whereas progress to a critical situation is observed in IgAV, GPA, EGPA, PAN, MPA, and KD. The management of such patients may require the dermatologist, because the correct interpretation of cutaneous lesions, an integral part of the clinical pattern, can provide substantial help in identifying the nature and phase of the disease. Dermatologic assistance may be essential in the treatment of lesions largely involving the skin.

The clinical features in an emergency situation requiring treatment in an intensive care unit mainly include abdominal and renal complications in IgAV; pulmonary and renal involvement in GPA; hemoptysis, respiratory and renal failure, myocarditis, and myocardial infarction in EGPA; renal insufficiency, cardiomyopathy, and GI bleeding and perforation in PAN; deterioration of renal function and respiratory failure in MPA; and cardiac involvement in the acute phase and subsequent development of coronary aneurysms in KD. The emergency situation can be particularly serious in PF, a disease that frequently evolves into DIC, a dramatic condition often culminating in death.

When present, dermatologic signs can be decisive in arriving at the correct diagnosis and treatment. Purpuric lesions mainly situated on the lower extremities, associated with polyarthralgia and abdominal pains, are almost always sufficient for a diagnosis of IgAV. Acral inflammatory manifestations, sometimes associated with polymorphic exanthema

and laterocervical lymphadenopathy in a child with persistent high fever, reliably indicate a diagnosis of KD; however, it can be more difficult to interpret cutaneous lesions in conditions suspected to be GPA, EGPA, PAN, or MPA. The histologic examination and other hematochemical data can provide other useful information for a diagnosis. PF deserves special consideration, because it can assume different clinical signs as a result of a meningococcal infection, especially in children, or as the evolution of a vascular pathology in adults. In both situations, necrotizing purpuric lesions are decisive for an accurate diagnosis.

The management and treatment of emergencies caused by systemic vasculitides must be carried out in an intensive care unit, where the patient can benefit from procedures aimed at improving the pulmonary ventilation and circulatory conditions and normalizing the hemodynamic and hydroelectrolytic imbalance. In this context, infusions of plasma (or its substitutes) and of whole blood may be useful. Regarding the use of specific drugs, corticosteroids are the first-line agents in GPA, EGPA, and PAN, diseases in which the association of cyclophosphamide can complete the emergency procedure. IVIG are fundamental in KD, where they can drastically reduce the onset of cardiologic complications. Other drugs, such as azathioprine, methotrexate, and the biologics, are more suitable for the prevention of relapses. The correction of coagulation alterations, fundamental in PF, requires much attention, because it must be carried out with drugs, such as heparin, protein C, AT III, and plasminogen activators, the use of which demands accurate monitoring of laboratory parameters and, above all, proven clinical experience.

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Emergency management of connective tissue disorders and their complications

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Collagen vascular diseases are complex multiorgan states of pathologic dysfunction. The collagen vascular diseases that most commonly result in emergency situations include systemic lupus erythematosus (SLE), dermatomyositis (DM), and scleroderma. This chapter will review emergency management of connective tissue disorders and their complications. In particular, the clinical and laboratory aids required for diagnosis, therapy, and prognosis will be reviewed. Because we assume that the reader has a basic understanding of the diseases, the chapter does not review them.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a complex state of systemic dysregulation that can affect any organ system. The noted writer Flannery O'Connor died at the age of 39, after surgery led to a reactivation and intensification of lupus that resulted in fatal kidney failure. As lupus can be a systemic disease, the most serious emergency management pertaining to it includes cardiovascular, pulmonary, hematologic, neurologic, renal, and gastrointestinal (GI) dysfunctions.¹ The activity of the disease compounded by concomitant infections (28.9% each) and/or thrombosis (261%), are major causes of mortality during the first 5-year follow-up period.²

The prevalence of SLE for 15- to 44-year-old white women has been estimated ranging from 18.3 to 52.2 cases per 100,000, and the U.S. population-based incidence of SLE can range from 3.4 to 7.6 per 100,000³ and twice that for 15- to 44-year-old black women.^{2,4}

In view of the relative rarity of SLE in men and in juvenile patients, SLE presents a higher rate of serositis and a lower rate of arthritis in men than in women. The risk of lupus nephritis is significantly higher in pediatric patients than in adults.² The Systemic Lupus International Collaborating Clinics (SLICC) classification criteria was published in 2012.⁵ This classification includes 11 clinical and 6 immunologic criteria (Table 24.1) (see Figures 24.1 through 24.5).

CARDIOVASCULAR DYSFUNCTION AND SLE Background

There are manifold intersections of cardiovascular dysfunction and SLE. Most striking is the risk of myocardial infarction, which is increased 50 times in women aged 35–44 years with lupus compared with an age- and sex-matched general population.⁶ Vascular events, not surprisingly, substantially increase the mortality rate in patients with SLE. In patients with long-standing lupus, the most common causes of death are due to cardiovascular diseases (CVDs).⁷

The basis for CVD in patients with lupus is complex and seems to involve a combination of inflammatory and immune mechanisms. In patients with SLE, oxidized lipid levels (such as oxidized low-density lipoprotein and proinflammatory high-density lipoprotein) are increased, adhesion molecules are upregulated, and cytokines (such as monocyte chemoattractant protein-1, tumor necrosis factor- α , interferon- γ , interleukin-1, interleukin-12, interleukin-17, adiponectin) are upregulated. These oxidized lipids are deposited in the walls of coronary vessels. Autoantibodies bind to the oxidized lipids, forming immune complexes, which provide a basis for the development of atherosclerosis. Some of the other theories include excess monocyte activation, the presence of antiphospholipid antibodies, dysregulation of the complement system, oxidative stress (homocysteine, paraoxonase), and variable antibody effects (to endothelial cells, antiatherogenic HDL, antilipoprotein lipase, oxidized LDL, C-reactive protein, etc.).⁸ The antibodies associated with SLE are shown in Table 24.2.

Men, increased age, hyperlipidemia, smoking, hypertension, and CRP are associated with a CVD risk among SLE patients. Several SLE-specific factors, including the disease activity and duration, possibly along specific manifestations and therapies, a presence of neuropsychiatric SLE, antiphospholipid antibodies, use of glucocorticoid and azathioprine, can cause a further increase for the risk of CVD in patients with SLE.⁹ The most common cardiac pathology is pericarditis with a reported prevalence of 60%. Valvular, myocardial, and coronary vessel lesions can also be manifested in SLE patients.¹⁰ Atherosclerotic CVD is common and is related to increased antiphospholipid antibodies.¹⁰ Most studies have reported a 2- to 10-fold increase in the risk of MI among SLE patients, with a greater increase in the relative risk generally observed in younger patients.⁹ Patients with lupus nephritis are at an increased risk for developing hypertension.¹⁰ The antiphospholipid syndrome may lead to ventricular dysfunction, intracardiac thrombi, myxomas, and pulmonary hypertension. The coronary arteries are not immune from the effects of vasculitis associated with lupus.

Diagnosis

Laboratory testing and imaging studies are utilized in the diagnosis of lupus-related cardiac disease, as in other cardiac diseases. Elevated lipid or C-reactive protein levels can be seen in patients with cardiac abnormalities associated with SLE. Mild pericarditis, valvular lesions, and myocardial dysfunction can be detected with echocardiography, a technique that is both sensitive and specific.

Table 24.1 Clinical and Immunologic Criteria Used in the Systemic Lupus International Collaborating Clinics (SLICC) Classification System

Clinical criteria

1. Acute cutaneous lupus, including lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of systemic lupus erythematosus, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus (psoriasiform or annular polycyclic lesions, or both)
2. Chronic cutaneous lupus, including classic discoid rash (localized and generalized), hypertrophic lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, and discoid lupus/lichen planus overlap
3. Oral ulcers or nasal ulcers
4. Nonscarring alopecia
5. Synovitis involving two or more joints and at least 30 min of morning stiffness
6. Serositis
7. Renal (urine protein-to-creatinine ratio [or 24 h urine protein]) representing 500 mg protein per 24 h or red blood cell casts
8. Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral and cranial neuropathy, acute confusional state
9. Hemolytic anemia
10. Leukopenia (<4000 cells per μL at least once) or lymphopenia (<1000 cells per μL at least once)
11. Thrombocytopenia ($<100,000$ cells per μL) at least once

Immunologic criteria

1. Antinuclear antibody concentration greater than laboratory reference range
2. Anti-double-stranded DNA antibody concentration greater than laboratory reference range (or twofold the reference range if tested by ELISA)
3. Anti-Sm: presence of antibody to Sm nuclear antigen
4. Antiphospholipid antibody positivity as determined by any of the following: positive test result for lupus anticoagulant, false-positive test result for rapid plasma reagin, medium-titre or high-titre anticardiolipin antibody concentration (IgA, IgG, or IgM), or positive test result for anti-2-glycoprotein I (IgA, IgG, or IgM)
5. Low complement C3, low C4, low CH50
6. Direct Coombs test in the absence of hemolytic anemia

Source: Petri M et al. *Arthritis Rheum* 2012;64:2677–2686.



Figure 24.1 Classic malar and facial erythema of systemic lupus erythematosus. (Courtesy of Kristen Biggers and Noah Scheinfeld.)

Therapy

Patients with SLE and CVD are approached similarly for non-SLE patients with heart disease. Lifestyle changes are recommended, including dietary and exercise counseling, plus encouragement for smoking cessation. Risk factors, such as increased lipid levels and elevated blood pressure, are targeted for reduction. Because patients with SLE are predisposed to clotting, it has been suggested that they should be placed on more aggressive anticoagulant therapy. All patients with SLE should take aspirin prophylactically, and more potent anticoagulants should be added to the treatment regimen as needed. Lupus pericarditis patients (79%) usually have a good response to steroids or NSAIDs.¹¹ Some theoretical evidences support a role for hydroxychloroquine in view of its antithrombotic and lipid-modifying properties.¹²

Course and Prognosis

Cardiovascular events in patients with SLE are less severe due to advances in therapy.

PULMONARY DYSFUNCTION AND SLE Background

The severity of pulmonary involvement varies from asymptomatic abnormalities to fulminant, life-threatening disease. The presence of pulmonary disease in SLE increases the risk of mortality.¹³ SLE is associated with respiratory pathology in all anatomic locations, including the pleura, pulmonary parenchyma, airways, vessels, and respiratory muscles. These disease processes can occur in one area of the respiratory system or in multiple places simultaneously. Pulmonary symptoms can wax and wane, further increasing the morbidity and mortality associated with lupus.

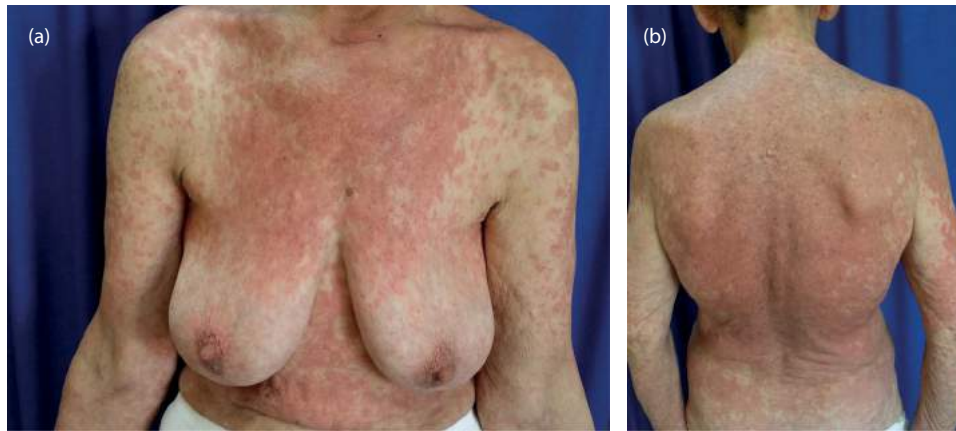


Figure 24.2 (a,b) Papulosquamous lesions of SLE lesions. (Courtesy of Ayşe Serap Karadag.)



Figure 24.3 Mucosal DLE lesions. (Courtesy of Ayşe Serap Karadag.)

The pathophysiology of pulmonary involvement in SLE is multifactorial and incompletely understood. It may encompass pulmonary vasculopathy, chronic thromboembolic disease (related to antiphospholipid antibody syndrome), left-sided heart disease, lung disease, or the combination of any of these factors.¹⁴

In SLE, the most common respiratory complaints are attributed to pleural disease, a pathology that affects up to 35% of patients.^{15,16} Pleuritic pain is said to be present in 45%–60% of patients, and pleural effusions (unilateral or bilateral) have been reported in 30%–50% of patients with SLE. Pericardial effusion and cardiomegaly may be present in up to 35% of patients.¹⁷ As in cardiovascular disease, lupus autoantibodies form immune complexes that are deposited in the pleura, resulting in injury. Other pulmonary disorders associated with SLE patients include acute lupus pneumonitis, alveolar hemorrhage pleural disease, pneumonia, diffusion impairments, diffuse alveolar hemorrhage, acute lupus pneumonitis, thrombosis, and pulmonary hypertension.^{10,18} Sudden-onset dyspnea and fever are characteristic of acute lupus pneumonitis and alveolar hemorrhage, which also results in hypoxemia and a chest x-ray demonstrating patchy alveolar infiltrates.^{18,19} Patients affected by diffuse alveolar hemorrhage (1%–5% of patients with SLE)^{20,21} have a 50%–90% risk of death attributed to the acute decrease



Figure 24.4 Lupus panniculitis. (Courtesy of Ayşe Serap Karadag.)



Figure 24.5 Lupus erythematosus tumidus lesions on the arm. (Courtesy of Ayşe Serap Karadag.)

Table 24.2 Antibodies Associated with Systemic Lupus Erythematosus

Antinuclear antibody (ANA)
Anti-double-stranded DNA (anti-dsDNA)
Anti-Smith (anti-Sm) antibody
Antianionic phospholipids antibodies
Mostly anticardiolipin (aCL)
Anti- β 2 glycoprotein 1 antibodies
Anti-C1Q antibodies
Anti-Ro (SSa) antibody
Anti-La (SSb) antibody

in hemoglobin levels.^{10,18,22,23} SLE therapy, including glucocorticoids or immunomodulatory agents, increases a patient's risk for developing pneumonia.^{24,25}

Pulmonary physiology is adversely affected in patients with SLE.²⁶ In a study comparing the lung function of 70 non-smoking, nonlupus patients with 70 age-matched, nonsmoking SLE patients showed normal lung function in 83% of subjects in the control group and only 33% in SLE patients.²⁶ Diffusion capacity of carbon monoxide in the lung (DLCO) is the most common adversely affected pulmonary function test and can be decreased even in the absence of a concomitant restrictive lung disease.^{26,27} As in vessels throughout the body, antiphospholipid antibodies can be deposited in the pulmonary vessels, causing thrombosis^{28,29} that results in fatal pulmonary hypertension, unresponsive to therapy.

Diagnosis

The clinical assessment of an SLE patient with respiratory symptoms requires a combination of history and physical examination, laboratory assessment, pulmonary function

testing, thoracic imaging modalities, bronchoscopy with bronchoalveolar lavage (BAL), and even a lung biopsy.³⁰ Imaging studies, including high-resolution computed tomography (CT) and magnetic resonance imaging (MRI), are useful in developing a diagnosis of lung disease in patients with SLE.^{31,32} CT scan has emerged as a very useful tool in the early diagnosis and management of SLE-associated pulmonary complications.³³

Therapy

Corticosteroids are the mainstays of treatment for SLE patients with pulmonary disease. It is especially effective in treating interstitial lung disease.^{34,35} Cyclophosphamide (500–1000 mg/m² intravenously [IV] every 4 weeks) can be used in resistant cases. Steroid-sparing agents, such as azathioprine and methotrexate, may be useful.³ Extremely resistant cases may benefit from plasmapheresis or IV immunoglobulin (IVIG). Rituximab is effective in increasing the effectiveness of traditional therapy, when used as an adjunct in patients who are unresponsive to traditional therapy alone. There are new biologics, such as belimumab, a monoclonal antibody that inhibits activating factor B cells (BAFF), also called an activator of B-lymphocytes (BlyS), that may be used in patients resistant to conventional therapy.³⁶

Course and Prognosis

SLE-associated pulmonary complications should be recognized and are important causes of morbidity and mortality. Ruling out infection and establishing the diagnosis of acute pulmonary involvement, such as alveolar hemorrhage, lupus pneumonitis, pulmonary embolism, or acute alveolitis in ILD, is vital, as these conditions require immediate treatment, with any delay resulting in increased risks of morbidity and mortality.³⁷

HEMATOLOGIC DYSFUNCTION AND SLE Background

Cytopenias, defined as an abnormally low number of different cell lineages, including leukopenia, anemia, lymphopenia, and thrombocytopenia, are common in SLE patients and can be among the presenting findings.³⁸ Several medications have been implicated in causing hematologic abnormalities, with CYC, azathioprine, and methotrexate being common causes of cytopenias.³⁸

Vasculitis and thrombosis are common manifestations of SLE. In addition to making antiphospholipid antibodies, patients with lupus can produce antiplatelet antibodies that precipitate thrombocytopenia.¹⁰

Diagnosis

The evaluation of cytopenias in SLE patients should start by repeating the complete blood count, followed by a detailed medical history. The antiphospholipids produced in patients with SLE include anticardiolipin antibodies, lupus anticoagulants, and anti- β 2 glycoprotein-1-specific antibodies.^{39,40} Lupus anticoagulant levels can be assessed via blood titers.^{39,40} If a patient is suspected of having a thrombus, confirmation may be obtained with imaging studies.

Therapy

Hematologic dysfunction in lupus is treated symptomatically with immunosuppressives for vasculitis and anticoagulants

for thrombosis. Due to their rapid and generally potent effects, corticosteroids are the initial treatment of immune-mediated hematologic abnormalities in SLE, particularly red cell aplasia, hemolytic anemias, and thrombocytopenia. When initially combined with corticosteroids, hydroxychloroquine has been shown to have an additive and steroid-sparing effect in the management of thrombocytopenia.⁴¹ Nonsteroidal therapy includes azathioprine and methotrexate.⁴² Thrombocytopenia caused by antideoxyribonucleic acid (anti-DNA) antibodies can be treated with IVIG or rituximab.^{38,43} Although the use of IVIG is well established for ITP in lupus patients, IVIG should be reserved for severe or unstable thrombocytopenia, refractory to corticosteroids.⁴⁴ Plasma exchange has been used in the severe hematologic manifestations of lupus,⁴⁵ including refractory thrombocytopenia, catastrophic antiphospholipid syndrome, pure red cell aplasia, and the hemophagocytic syndrome. Rituximab is effective in SLE patients with such hematologic involvement as autoimmune hemolytic anemia, thrombocytopenia, and TTP.^{38,46}

Course and Prognosis

Increased risk of thrombotic events is especially dangerous in pregnant women and can be fatal for both the mother and the fetus.

NEUROLOGIC DYSFUNCTION AND SLE Background

Rarely, SLE is associated with neuropsychiatric conditions, including organic brain syndrome, seizures, cerebrovascular accidents, psychosis, peripheral neuropathy, acute confusional state, anxiety disorder, headache, cognitive dysfunction, mood disorder, and chorea.¹⁰ Even less common neuropsychiatric manifestations are aseptic meningitis, demyelinating syndrome, myelopathy, movement disorder, pseudotumor cerebri, Guillain-Barré syndrome, athetosis, and cerebral venous sinus thrombosis.^{10,47} Some neurologic disorders that may be associated with SLE are related to the deposition of antiphospholipid and antiribonucleoprotein (anti-RNP) antibodies.⁴⁸ Raynaud phenomenon and livedo reticularis can occur with an increased risk of neuropsychiatric manifestations in patients with SLE.⁴⁹

Diagnosis

In patients with SLE-associated neuropsychiatric disorders, a spinal tap may show increased cell counts, elevated protein levels, and increased immunoglobulins in the cerebrospinal fluid.⁵⁰ Less invasive diagnostic techniques may be utilized to detect cranial bleeds, thrombosis, vasculitis, and inflammation, and include EEG, CT, MRI, transcranial Doppler monitoring, and digital subtraction angiography (particularly for vasculitis).^{47,50} There may be an association of antiribosomal P protein antibodies in serum and CSF with NPSLE, with a strong relationship with psychosis and severe depression.^{47,51}

Therapy

In patients with SLE, neuropsychiatric complications are controlled by treating the underlying pathology, as in the other organ systems.¹⁰ Intermittent intravenous cyclophosphamide may be more successful than intravenous methylprednisone (95% versus 54%). New promising targeted immunosuppressive therapies, such as B-lymphocyte depletion with anti-CD20

antibody, may be used alone or in combination with cyclophosphamide.⁵² IVIG and plasmapheresis are often used sooner in neuropsychiatric conditions associated with SLE than when other organ systems are affected due to the severe complications that can result from inadequate therapy.¹⁰

Course and Prognosis

Patients with SLE associated with neuropsychiatric conditions resistant to IVIG and/or plasmapheresis therapy should be given high-dose intravenous methylprednisolone to bring the disease rapidly under control.^{53,54}

RENAL DYSFUNCTION AND SLE Background

The most common systemic complication of SLE is renal disease.¹ Lupus nephritis (LN) refers to inflammation of the kidney that encompasses diverse patterns of renal diseases including glomerular, tubulointerstitial, and vascular pathologies.⁵⁵ LN may be present in approximately 60% of adult patients, and around 25%–50% of SLE patients present with clinical renal diseases at the time of diagnosis.⁵⁶ LN tends to occur more frequently in African Americans, and overall less favorable prognosis is also notable within this population. Other factors associated with poor outcomes include socioeconomic factors, age greater than 30 years, gender, duration of SLE diagnosis, uncontrolled hypertension, anemia, elevated serum creatinine, high rate of decline in glomerular filtration rate, low C3 complement, and chronic renal scarring.⁵⁷ Anti-DNA antibodies form complexes with double-stranded DNA polynucleotide antigens that deposit in the small vessels of the kidney, which is the major cause of lupus nephritis. Type III sensitivity reactions, during which antibodies bind with fixed antigens to form a complex, may also play a role in lupus nephritis. It has also been hypothesized that sensitized T cells may contribute to renal pathology in lupus patients.

Diagnosis

The presence of proteinuria (>0.5 g/d) or cellular casts is required to diagnose renal involvement in patients with SLE, as defined by the American College of Rheumatology.⁵⁸ Lupus nephritis and renal dysfunction can be further complicated by the presence of antiphospholipid antibodies, low complement (C3) levels, thrombocytopenia, anemia, or hypertension, and death may result.⁵⁹ Immune complexes composed of DNA double-stranded polynucleotide antigens and anti-DNA antibodies may be elevated in patients with lupus nephritis. In addition to serum testing, a renal biopsy may be performed to diagnose focal proliferative, diffuse proliferative, or membranous glomerulonephritis.⁵⁸

Therapy

As in most patients with lupus, corticosteroids are the mainstay of treatment for patients with lupus nephritis with the addition of mycophenolate mofetil (MMF) and azathioprine to the therapeutic regimen.⁶⁰ All patients with LN of any class are treated with hydroxychloroquine, unless there is a specific contraindication to the drug. There is some evidence that hydroxychloroquine may protect against the onset of LN, relapses of LN, and end-stage renal disease.⁶¹ IV cyclophosphamide (0.5 g/m²) may be necessary for refractory renal disease or in patients with

diffuse proliferative lupus nephritis. When this treatment is selected, cyclophosphamide is infused monthly for 6 months, and then at regular intervals for a full year following remission.⁶² The use of rituximab as an off-label treatment for LN has been increasing, but rituximab may not be as effective as other traditional therapies for induction or maintenance, and rituximab showed no superiority over placebo in terms of efficacy, despite its suitable safety profile.^{63,64} Belimumab has been found to be effective in reducing flares, disease severity, and proteinuria in SLE patients.⁶⁵

Course and Prognosis

LN is a severe complication of SLE with high morbidity and mortality rates in untreated cases⁶³ and can progress to end-stage kidney disease in 5%–10% of patients within 10 years after the diagnosis. If LN occurs early in the course of SLE, it is considered as a major predictor of poor prognosis.⁶⁵ In patients who meet the criteria for SLE-associated renal disease, their survival is largely determined by their creatinine levels.^{1,66} Patients with SLE-associated renal disease may suffer from end-stage renal disease and require dialysis.

GI DYSFUNCTION AND SLE

Background

GI dysfunction is common in patients with SLE, and over a lifetime affects 60%–70% of those patients. The liver is particularly susceptible in patients with lupus and antiphospholipid syndrome. Portal hypertension, cirrhosis, biliary cirrhosis, autoimmune hepatitis, Budd-Chiari syndrome, hepatic infarct, and hepatic-venoocclusive disease are all possible associated conditions. Other GI manifestations include vasculitis throughout the GI tract, oral ulcers, dysphagia, intestinal ischemia, infarction or bleeding, splenic infarction, and acute pancreatitis. Rarely, there may be esophageal, intestinal, pancreatic and cholecystic involvement, intestinal pseudoobstruction, malabsorption, protein losing enteropathy, peritonitis, and ascites.⁶⁷ Corticosteroids used therapeutically can have adverse effects on the GI tract by causing spontaneous hemorrhage.

Diagnosis

Lupus patients can present with abdominal pain, anorexia, hemorrhage, nausea, and vomiting. Clinical testing may yield little as far as etiology.

Therapy

Most SLE-related gastrointestinal complications are caused by vasculitis and immune complex deposition, which usually respond to corticosteroids and immunosuppressive agents.⁶⁸ Patients with chronic symptoms can be treated with corticosteroids or anticoagulants. Those with an acute presentation should be assessed quickly, as emergent surgery is usually the treatment of choice. Exploratory surgery is often required in patients with suspected peritoneal collections or GI perforations. In cases of perforation or bowel ischemia, the affected area should be surgically resected as the first step in treatment. Supportive measures, such as bowel rest, nutritional support, antimicrobials, and prokinetic medications are helpful in facilitating functional recovery and improving the outcome.⁶⁸

Course and Prognosis

Early diagnosis and timely treatment are critical for improving the prognosis.⁶⁸ Lupus patients with acute GI symptoms can rapidly progress to life-threatening status without immediate intervention.

NEONATAL LUPUS ERYTHEMATOSUS

Background

Women with lupus have several autoantibodies (Table 24.2) (anti-SS-A/Ro, anti-Sjögren syndrome-B [anti-SS-B/La], and/or anti-ribonuclear protein [anti-RNP])⁶⁹ that are capable of crossing the placenta. A pregnant woman with lupus can pass these antibodies on to her fetus, resulting in neonatal lupus erythematosus (NLE). After delivery, the infant can present with dermatologic signs similar to those seen in adults with SLE.³⁴ The most common presentation is a nonscarring, nonatrophic skin lesion resembling subacute cutaneous LE. Infants may have no skin lesions at birth but develop them during the first weeks of life. Periorbital erythema, referred to as “raccoon eye” or “owl eye,” is a very common characteristic finding. Cardiac, hematologic, hepatobiliary, central nervous, and pulmonary systems may also be involved.⁷⁰

Diagnosis

Screening of infants with NLE and mothers of patients suspected of having these antibodies (antinuclear, anti-double-stranded DNA, anti-Ro/SSA, anti-La/SSB, and anti-U1-RNP antibodies) is strongly recommended.⁷⁰ M-mode fetal echocardiograms and Doppler ultrasounds performed between 18 and 24 weeks' gestation can be useful in detecting atrioventricular (AV) heart block or atrial arrhythmia in a fetus with NLE. If a heart block is detected, these studies can also determine the degree of the block (first, second, or third), as well as any valvular (especially tricuspid) regurgitation or other congenital anatomic cardiac anomalies.

Pregnant women with lupus should receive fetal echocardiograms throughout their pregnancies to facilitate the early identification of heart block.

Therapy

When a first- or second-degree AV block has been identified in a fetus with NLE, corticosteroids should be administered to the mother in an attempt to eliminate the heart block. The reversal of third-degree heart block with corticosteroids is highly unlikely. Other treatments include steroids in conjunction with IVIG and plasmapheresis.⁶⁹

Course and Prognosis

The morbidity and mortality of neonatal SLE depend on organ system involvement.⁷⁰ Unfortunately, completely unremarkable echocardiograms can change in 1 week to an echocardiogram demonstrating cardiomyopathy or third-degree AV block without warning. Only 80% of infants with NLE-related first-degree heart block survive the first year. Of those children who do survive, the majority of them will need a pacemaker.

DM

DM is an inflammatory myopathy, the nature of which is idiopathic. The manifestations of this disease include progressive



Figure 24.6 Gottron sign of dermatomyositis: reddish plaques on the joints and on the fingers. (Courtesy of Kristen Biggers and Noah Scheinfeld.)

symmetrical proximal muscle weakness and dermatologic manifestations.⁷¹ Gottron papules (see Figure 24.6), Gottron sign, and a heliotrope eruption (see Figure 24.7) are very diagnostic skin lesions in DM. The occasional skin lesions are facial erythema, periungual changes, mechanic's hand, shawl sign, V-neck sign, flagellate erythema, calcinosis cutis, and poikiloderma.⁷² Table 24.3 shows the cutaneous manifestations of dermatomyositis.⁷³

Additional organ systems affected in systemic DM are the GI tract, lungs, and blood vessels.⁷⁴ The systemic manifestations are responsible for emergent situations in patients with DM.⁷⁴ Ricky Bell, a football player, who was a standout running back for the University of Southern California Trojans, and played for Tampa Bay and San Diego in the National Football League, died from heart failure caused by DM. To be diagnosed with DM, a person must present with at least three of the following clinical criteria: (1) symmetric proximal muscle weakness determined by physical examination; (2) muscle biopsy pathology (degeneration, regeneration, necrosis, phagocytosis, and an interstitial mononuclear infiltrate); (3) elevated creatine kinase, aldolase, lactate dehydrogenase, aspartate aminotransferase, or alanine aminotransferase, all of which point to muscle involvement; (4) the electromyographic triad of short, small,

polyphasic motor unit potentials; fibrillations, positive sharp waves, and insertional irritability; and bizarre, high-frequency repetitive discharges; or (5) the typical skin eruption of DM, including a heliotrope eruption and Gottron sign/papules.⁷⁵ In all manifestations of the disease, creatine kinase levels may be used to track the progression of or the response to treatment of DM.⁷⁶ Specific serum antibody levels can be drawn to aid in the diagnosis of DM (Table 24.4).^{72,76}

Muscle involvement may be tracked using electromyography, ultrasonography, or MRI.⁷⁷ Additionally, a muscle biopsy can be performed to assess muscle involvement and will show immune-mediated necrosis and regenerating fibers. On skin biopsy, mucin in the background of interface dermatitis is commonly seen histologically.⁷⁸

Patients with DM have about a fivefold increased risk for developing a malignancy than the general population. The increased risk of lymphatic/hematopoietic malignancies is especially prominent with the highest incidence, which is seen more than 22-fold higher in patients with DM than in the general population.⁷⁹ Prognostic factors for mortality are being a man and having heart and lung involvement. Responsiveness to immunoglobulin treatment, intravenously or subcutaneously, may permit a better survival.⁸⁰

GI TRACT AND DM Background

DM can affect much of the GI tract, especially the esophagus and intestines. Esophageal disease is common in patients with DM (15%–50%) and most often stems from problems associated with weakness of the cricopharyngeal striated muscles or dysfunction of the lower part of the esophagus.⁸¹ Dysphagia to solids and liquids occurs in patients with myositis. Due to decreased pharyngoesophageal muscle tone, patients can develop nasal speech, hoarseness, nasal regurgitation, and aspiration pneumonia. Of all patients with DM, approximately 30% of them will die from complications associated with aspiration pneumonia.⁸¹ The other DM-related presentations include tongue weakness, flaccid vocal cords, poor palatal motion, and pooling of secretions in the distended hypopharynx.⁸² Less frequently (and especially in young patients with DM), ulceration, perforation, or hemorrhage may occur in the GI tract as a result of vasculopathy in that area.⁸³

Diagnosis

DM can cause inflammation in the GI tract, leading to patients presenting with reflux esophagitis, abdominal pain, and cycles of constipation alternating with diarrhea.⁸⁴ A traditional GI workup, including CT, MRI, colonoscopy, and barium studies are used, as in other GI diseases, to assess the severity of disease.⁸⁵

Treatment

Surgical intervention and immunosuppressives are the standard of care for treating GI disease in DM. Anti-TNF therapy can be considered in refractory DM, although its efficacy has been disputed.⁸⁶ IVIG may be successful in treating resistant esophageal disease that might otherwise be life threatening.⁸⁷



Figure 24.7 Heliotrope rash. (Courtesy of Ayşe Serap Karadag.)

Table 24.3 Cutaneous Manifestations of Dermatomyositis

Pathognomonic skin lesions of DM

1. Gottron papules

Papules having a violaceous hue overlying the dorsal-lateral aspect of interphalangeal and/or metacarpophalangeal joints.

2. Gottron sign

Symmetrical macular violaceous erythema with or without edema overlying the dorsal aspect of the interphalangeal/metacarpophalangeal joints, olecranon processes, patellae, and medial malleoli.

Highly characteristic skin lesions of DM

1. Periorbital violaceous (heliotrope) erythema with or without associated edema of the eyelids and periorbital tissue

2. Grossly visible periungual telangiectasia with or without dystrophic cuticles

3. Symmetrical macular violaceous erythema overlying the dorsal aspect of the hands and fingers (where it can track the extensor tendon sheaths), extensor aspects of the arms and forearms, deltoids, posterior shoulders and neck (the shawl sign), V-area of anterior neck, and upper chest, central aspect of the face and forehead

Compatible skin lesions of DM

1. Poikiloderma vasculare atrophicans (poikilodermatomyositis)

2. Circumscribed violaceous erythema with associated telangiectasia, hypopigmentation, hyperpigmentation, and superficial atrophy most commonly found over the posterior shoulders, back, buttocks, and V-area of the anterior neck and chest.

3. Calcinosis cutis

Source: Euwer RL, Sontheimer RD. *Curr Opin Rheumatol* 1994;6:583–589.

Table 24.4 Autoantibodies in Dermatomyositis

Antibodies	Clinical association
Anti-Mi-2	Classical DM
Anti SAE	Adult DM
Anti-p155/140 (Anti-TIF γ/α)	Cancer-associated DM, adult DM, juvenile DM
Anti-MJ (NXP-2)	Juvenile DM, severe calcinosis
Anti-t-RNA synthetase (anti ARS)	Anti synthetase syndrome
Anti-Ro/SSA	Anti synthetase syndrome
Anti Jo-1	Anti synthetase syndrome
Anti-PMS1	Adult DM
Anti-MDA 5	Classical DM, skin ulcer

Source: Muro Y, Sugiura K, Akiyama M. [published online June 23, 2015]. *Clin Rev Allergy Immunol*. doi:10.1007/s12016-015-8496-5. Targoff IN. *Rheum Dis Clin North Am* 2002;28:859–890.

Note: ARS: anti-aminoacyl-tRNA synthetase; SAE: anti-small ubiquitin-like modifier activating enzyme; (TIF)-1 γ : antitranscriptional intermediary factor.

Course and Prognosis

The pharyngeal muscle weakness in patients with DM causes loss of control of foods and can result in aspiration. Due to the aspiration risk, these patients may be placed on a feeding tube.⁸⁸ Patients with esophageal muscle weakness do not respond well to therapy; therefore, they have a poor prognosis.^{81,88}

PULMONARY SYSTEM AND DM

Background

Pulmonary disease is a fairly common occurrence in patients with DM (15%–30%), and in 50% of these patients, it is the first presenting sign of the disease.⁸⁵ The majority of DM patients presenting with respiratory disease (60%) have an insidious onset. Others (25% of patients) have an acute onset of signs, and 15% of patients have an infraclinical onset that presents as an incidental finding on exam. Patients with amyopathic DM can have fatal pulmonary diseases or pulmonary complications.⁸⁹

Pulmonary inflammation is the leading pathology in lung diseases in patients with DM.⁸⁵ Respiratory muscle

weakness leads to hypoventilation, and esophageal muscle weakness leads to aspiration, both of which result in inflammatory processes. Additionally, the treatment for DM itself, usually immunosuppressive therapies, can leave the patient susceptible to opportunistic infections or hypersensitivity pneumonitis.⁸⁵

Pulmonary diseases associated with DM include pulmonary hypertension,⁸⁴ pneumothorax, pneumomediastinum, interstitial lung disease, and subcutaneous emphysema.⁹⁰

Intestinal lung disease (ILD) may lead to such complications as pulmonary hypertension or cor pulmonale that can be rarely rapidly progressive and fatal.⁹¹ Diffuse alveolar damage, respiratory bronchiolitis, bronchiolitis obliterans, and pneumonia (desquamative interstitial and nonspecific interstitial) are all interstitial pulmonary diseases caused by fibrosing alveolitis in DM.⁸⁹

Diagnosis

Patients with DM and associated pulmonary disease may present with the symptoms of exertional dyspnea and non-productive cough, as well as the clinical sign of bibasilar fine crackling rales.⁸⁹ Because pulmonary physiology can be affected, further studies should include pulmonary function testing, which demonstrate decreased DLCO and a restrictive pattern.⁸⁹ A high-resolution CT scan should be performed with the pulmonary function tests as part of the initial workup. Pulmonary function tests and CT scans should be repeated regularly to assess treatment effectiveness and progression of disease.

Antisynthetase antibodies (Table 24.5) can be seen in DM patients with pulmonary disease.⁷⁶ Patients with an acute onset of interstitial pulmonary fibrosis and dramatic polymyositis that is resistant to therapy should be considered for antisynthetase syndrome.⁹⁰ This often fatal syndrome can be seen in patients with DM and antisynthetase antibodies who also suffer from fever, interstitial pulmonary fibrosis, Raynaud phenomenon, arthritis, and mechanic's hand.⁷¹ The presence of anti-MDA5 antibody is significantly associated with ILD, being related to a poor pulmonary outcome and a poor survival rate in classic DM.⁹² Additionally, patients with pulmonary fibrosis may express the myositis antibody, anti-Se.⁷⁶

Table 24.5 Antisynthetase Antibodies

Anti-Jo
Anti-PL-7
Anti-PL-12
Anti-OJ
Anti-EJ
Anti-KS
Anti-Zo
Anti-YRS

Source: Hallowell RW, Ascherman DP, Danoff SK. *Semin Respir Crit Care Med* 2014;35:239–248.

Therapy

As in patients with other forms of DM, corticosteroids remain the treatment of choice for patients suffering from pulmonary disease.⁹³ High-dose IV corticosteroids can be administered in severe cases with acute onset. If corticosteroids fail to alleviate symptoms, methotrexate can be added to the regimen or administered alone as a second-line agent.⁹⁴ Azathioprine, cyclophosphamide, chlorambucil, cyclosporine, MMF, tacrolimus, or chlorambucil can be used as third-line treatments.⁹⁴ Interstitial pulmonary disease in DM responds well to cyclosporin A therapy.^{95,96} IVIG, rituximab, and adalimumab may be used in resistant cases.^{87,97}

Course and Prognosis

The biggest factor determining survival rates in patients with DM and the antisynthetase syndrome is the presence of ILD, and most of the deaths in the DM group are attributable to rapidly progressive lung disease.⁹⁸ Unfortunately, for patients with pulmonary symptoms in the context of DM, their prognosis is poor.⁸⁵ Pulmonary fibrosis results in interstitial lung disease and pulmonary hypertension, both of which are often fatal. The chronic respiratory insufficiency resulting from interstitial lung disease is fatal in 30%–66% of patients.⁸⁴

CARDIOVASCULAR DISEASE AND DM

Background

Although cardiac disease is rarely a complication of DM, when it presents, it is usually fatal.⁸⁴ Inflammatory myositis can result in cardiac dysfunction as can vasoconstriction from vasculitis.⁹⁹ DM-associated cardiac complications are cardiomyopathies, atherosclerotic cardiovascular disease, coronary heart disease, hypertension, ventricular dysfunction, angina, and myocardial infarction.¹⁰⁰

Diagnosis

When a patient with DM presents with cardiac symptoms, the same tests should be performed as would be on any patient presenting with cardiac symptoms. These standard cardiac tests should reveal the location and degree of involvement of heart muscle. No such strong correlations between autoantibodies and heart disease in myositis have been reported.¹⁰² Additional testing could include blood-vessel biopsies. A biopsy of a vessel affected by DM should demonstrate scarring in the vessel wall, with or without associated fibrosis.

Treatment and Prognosis

For those patients who suffer from DM-associated cardiac disease, few treatment options are available, and those that are available are usually unable to alleviate disease. Having pulmonary and cardiac symptoms simultaneously greatly increases a patient's risk of fatality.⁸⁴ Neurologic symptoms can appear in children with DM due to inflammatory changes in the blood vessels.⁸³ These vasculitis-associated conditions include stroke, hemiparesis, seizures, and pseudoseizures.⁸³

SCLERODERMA (SYSTEMIC SCLEROSIS)

Scleroderma, by definition, is a systemic disease and can have adverse effects on the GI, renal, and pulmonary systems. The disease is characterized by autoantibody production and small-vessel vasculopathy with varying degrees of internal organ and skin fibrosis.¹⁰¹ The respiratory system is most commonly the location for pathology that can be emergently life threatening in patients with systemic sclerosis (SS).¹⁰¹ In fact, Paul Klee (the noted Swiss artist who had scleroderma) died of scleroderma-related pulmonary fibrosis that led to respiratory failure. It can affect the skin and lead to hardening of the skin, nail fold changes, calcinosis, and sclerodactyly (Figure 24.8). Unfavorable prognostic factors are male sex, age at disease



Figure 24.8 Scleroderma of the hand demonstrating sclerodactyly. (Courtesy of Kristen Biggers and Noah Scheinfeld.)

Table 24.6 Scleroderma Diagnostic Criteria (EUSTAR Final List of Criteria for the Very Early Diagnosis of Systemic Sclerosis [VEDOSS])

Criteria considered as having a high clinical relevance for the very early diagnosis of SSc	Raynaud phenomenon Puffy swollen digits turning into sclerodactyly Abnormal capillaroscopy with scleroderma pattern Positive anti-CENP Positive anti-topo I
Criteria considered as leading to an early referral	Raynaud phenomenon Puffy fingers Positive antinuclear antibodies

Source: McCray CJ, Mayes MD. *Curr Allergy Asthma Rep* 2015;15:25.

onset older than 65 years, digital ulcers, interstitial lung disease (ILD), pulmonary hypertension, heart involvement, scleroderma renal crisis (SRC), presence of antitopoisomerase I and absence of anticentromere antibodies, and an active capillaroscopic pattern.¹⁰² The diagnostic criteria of scleroderma are shown in Table 24.6.¹⁰³

PULMONARY DISEASE AND SCLERODERMA Background

Pulmonary fibrosis, a normal manifestation of scleroderma, results in interstitial fibrosis of the lungs. Vasculitides resultant from SS and interstitial fibrosis can both lead to the development of pulmonary hypertension, as seen in 5%–50% of patients with scleroderma.^{101,102}

Diagnosis

Patients present with dyspnea on exertion as their initial manifestation of pulmonary hypertension. Clinically, pulmonary hypertension is tested while the patient is exercising and is defined as an increase in mean pulmonary arterial pressure to greater than 25 mm Hg.^{101,102}

Therapy

Early stages of scleroderma-related pulmonary hypertension are treated, as is hypertension in most disease states, with vasodilators. The mainstay of treatment for pulmonary hypertension includes endothelin receptor antagonists (ERAs)¹⁰⁴ and prostanoids.¹⁰⁵ Scleroderma consensus guidelines recommend endothelin ERAs in mild pulmonary hypertension as a first-line treatment, combination ERA and PDE5i as second-line treatment, and prostanoids as third-line treatment.¹⁰⁶ For severe disease, prostanoids are recommended as a first-line treatment. A newer, more stable compound, treprostinil, is administered subcutaneously¹⁰⁷ and is more effective than epoprostenol at relieving pulmonary symptoms and decreasing arterial pressure and vascular resistance.¹⁰⁸ Bosentan, an oral endothelin antagonist, and sildenafil, an oral cyclic guanosine 3', 5'-monophosphate phosphodiesterase type five (cGMP PDE5) inhibitor, have been effective in relieving the manifestations of pulmonary hypertension in patients with scleroderma.¹⁰⁴ Two newer drugs for treatment of pulmonary hypertension include¹⁰¹ macitentan, a dual-receptor ERA that significantly reduces morbidity and mortality in pulmonary hypertension,¹⁰⁹ and riociguat, a soluble guanylate cyclase stimulator that is directed toward pulmonary hypertension.

For pulmonary fibrosis, immunosuppressives are the treatment of choice. In cases of severe pulmonary fibrosis, 100 mg/d doses of cyclophosphamide have been shown to improve both forced vital capacity and overall survival.¹¹⁰ Some investigators believe, however, that corticosteroids have no positive effect on lung function.¹¹¹ Lung transplantation is a potentially life-saving option for selective SSc patients with severe ILD and/or PAH.¹⁰¹

Course and Prognosis

Scleroderma-related pulmonary disease still has high mortality and morbidity rates. In patients with scleroderma-related pulmonary disease, their initial symptom of dyspnea on exertion increases in severity. Such patients may develop right-sided heart failure.¹⁰⁷

RENAL DISEASE AND SCLERODERMA Background

The most common systemic manifestation in scleroderma, occurring in 25% of patients, involves the renal system.⁷⁴ Renal crisis is more prevalent in scleroderma patients, whose symptoms include the presence of antiribonucleic acid (RNA) polymerase III antibody in the serum, rapidly progressive skin thickening,¹¹² pericardial effusion, arrhythmias, and anemia.¹¹³ Additionally, the treatment for SS, corticosteroids, especially cyclosporine, can precipitate renal crisis.¹¹³ Renal crisis presents within the first 4 years of diagnosis of scleroderma in the majority of patients (75%), rarely occurring in patients suffering from SS for many years.¹¹⁴

Patients with SS develop narrowed arteries and arterioles.¹¹³ This phenomenon greatly impacts upon the kidneys and can result in renal crisis.¹¹³ A positive-feedback loop occurs that significantly restricts the blood flow to the kidneys. Initially, collagen deposits in arteriole walls, decreasing their diameter and limiting blood flow to the kidneys. The juxtaglomerular apparatus recognizes the postglomerular decrease in blood pressure and releases renin.¹¹³ This release of renin activates the renin-angiotensin system, resulting in increased secretion of angiotensin II. Angiotensin II causes vasoconstriction of the afferent and efferent arterioles in the kidney. This vasoconstriction further limits blood flow, leading to ischemia and renal crisis.¹¹³ The spectrum of renal complications in systemic sclerosis includes scleroderma renal crisis (SRC), normotensive renal crisis, antineutrophil cytoplasmic antibodies-associated glomerulonephritis, penicillamine-associated renal disease, and reduced renal functional reserves manifested by proteinuria, microalbuminuria, and/or isolated reduction in glomerular filtration rate.¹¹⁵

Diagnosis

There are recognized diagnostic criteria for renal crisis in patients with scleroderma. Patients usually present with a dramatic spike in arterial blood pressure with concomitant symptoms of headaches, visual disturbances, and seizures, and signs of thrombocytopenia, microangiopathic hemolytic anemia, accelerated oliguric renal failure, pericardial effusion, and congestive heart failure.¹¹² The diagnostic criteria for hypertensive scleroderma renal crisis are elevated serum creatinine, proteinuria, hematuria, thrombocytopenia, and hemolysis.¹¹² The majority of patients (90%) present with hypertension,¹¹²

and nearly all of them have elevated renin plasma levels.¹¹³ Lipocalin-2 may be involved in renal dysfunction and dermal fibrosis of SSc.¹¹⁶ Anti-RNA polymerase III antibodies are strongly positive in the diagnosis of scleroderma renal crisis in the absence of skin disease.¹¹⁷

Therapy

The only effective treatment for people in renal crisis is an angiotensin-converting enzyme (ACE) inhibitor to help dampen the effects of the increased plasma renin levels.¹¹⁴ Angiotensin II receptor blockers (ARBs) can safely be added once ACEi dose has been maximized, but ARBs alone are insufficient to control SRC without ACEi.¹¹⁸

Course and Prognosis

Although ACE inhibitors have been shown to decrease mortality and morbidity associated with renal crisis,¹¹⁵ some patients may require dialysis. In general, renal crisis is viewed as an indicator of poor prognosis in patients with SS.

MIXED CONNECTIVE TISSUE DISEASE

Background

Patients with symptoms that overlap those of SLE, SS, and DM are classified as having a mixed connective tissue disease. The most common clinical manifestations of mixed connective tissue disease include Raynaud phenomenon, arthralgias, swollen joints, esophageal dysfunction, muscle weakness, and finger-sausage-like appearance, together with the presence of anti-ribonucleoprotein (RNP) antibodies.¹¹⁹ As would be expected, pulmonary disorders in patients with mixed connective tissue disease resemble those seen in patients with lupus, DM, and scleroderma. These disorders include interstitial fibrosis (20%–65%), pleural effusion (50%), pulmonary hypertension (10%–45%), and pleurisy (20%). Other less common pulmonary features of MCTD include pulmonary vasculitis, thromboembolism, aspiration pneumonia, miscellaneous infections, hemorrhage, obstructive airway disease, respiratory failure (hypoventilatory), and diaphragm muscle weakness. The disease can be serious with development of pulmonary, kidney, cardiovascular, gastrointestinal, and central nervous system manifestations.¹¹⁹

Diagnosis

The presence of anti-uridine-rich RNA-small nuclear ribonucleoprotein (U1-snRNP) antibodies is required to diagnose a patient with mixed connective tissue disease. Other autoantibodies frequently observed in MCTD patients are antiphospholipids (aCL, anti-2GPI), anti-Ro, AECA, rheumatoid factor (RF), as well as anticyclic citrullinated peptides (anti-CCPs).¹²⁰

Treatment

Some patients may have mild self-limited disease, whereas others may develop life-threatening disease with severe major organ involvement.¹²¹ As in patients with DM, corticosteroids are the gold standard for treatment of pulmonary symptoms in patients with mixed connective tissue disease. In any case, therapy should be individualized for each patient to address the specific organ involvement and the severity of underlying disease activity. Corticosteroids and cytotoxic agents, such as cyclophosphamide,

are the most frequently administered immunosuppressants. Hydroxychloroquine, methotrexate, and different types of vasodilators have also been used with varying degrees of success.^{119,122}

COURSE AND PROGNOSIS

The prognosis for patients with pulmonary hypertension in the setting of mixed connective tissue disease is similar to those with pulmonary hypertension associated with other collagen vascular disorders: grim. Despite aggressive treatment, usually symptomatic relief is briefly attained before the disease contributes to the patient's mortality.¹²²

CONCLUSIONS

Because collagen vascular diseases are widely systemic, affecting many organ systems, their successful treatment is as complex as the diseases themselves. Most important to treatment success is early recognition and proper diagnosis. Early therapy may prevent possible life-threatening emergencies in the future. While many patients may initially present with dermatologic manifestations, it is important for the physician to look beyond the patient's primary complaint to the possible outcomes of systemic manifestations.

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Skin signs of systemic infections

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Many systemic infections have cutaneous presentations that sometimes are nonspecific. These cutaneous signs and symptoms may be helpful in making the proper diagnosis, prescribing the appropriate therapy, and assisting in prevention. Some clinical manifestations of systemic infections highlight the possible infectious etiology for unusual cutaneous lesions. Bacterial systemic infections may be more common in remote areas of the world; these same bacterial diseases also may be seen, however, in travelers or immigrants from these areas. Some of these infections, such as plague and melioidosis, are potential biologic weapons used for bioterrorism.

MELIOIDOSIS

Melioidosis is a highly invasive and resistant infection caused by the gram-negative bacterium *Burkholderia pseudomallei*, which is synonymous with the old nomenclature *Pseudomonas pseudomallei*. The first reported cases of *P. pseudomallei* infection were initially known as Whitmore disease. In 1911, a British pathologist, Captain Alfred Whitmore (1876–1946), described a case of pneumonia in a young boy in Burma, where *P. pseudomallei* was isolated as the causative agent.¹ The term “melioidosis” was subsequently used in 1921. It is derived from the Greek word “melis” meaning “a distemper of donkeys,” because it resembles glanders, which causes mainly pulmonary disease in asses.² This infection is endemic in Southeast Asia and North and Central Australia and peaks during the monsoon seasons.³ The disease in those regions often causes septicemia and death. Melioidosis also occurs sporadically in temperate countries and is mostly imported by travelers.⁴ Melioidosis contributes from 20% to 40% of deaths due to community-acquired septicemia in Northeast Thailand, especially in rice farmers.⁵ In Singapore, the disease is uncommon, even though a significant percentage of the population has been exposed to *B. pseudomallei*.⁶ The overall mortality rate remains near 45%, despite antimicrobial therapy. Before the antibiotic era, 95% of patients died.² *B. pseudomallei* is distributed in soil and surface water; thus, infection can be spread via inoculation through cutaneous abrasions. Inhalation or ingestion of contaminated bacilli materials is less frequent. Melioidosis is strongly associated with diabetes mellitus (50% of Asian patients) and is four times more common in men than in women.

Clinical Features

Clinical manifestations develop after an incubation period, which varies from a few days to several months or years. Patients develop high fever and rigors, as well as occasional confusion, stupor, jaundice, and diarrhea. The clinical spectrum includes five possible forms of presentations:

- Acute fulminant septicemia (fatal within days)
- Subclinical form⁷
- Subacute presentation (more likely associated with skin involvement)
- Acute presentation (also, more likely associated with skin involvement)
- Relapsing-remitting course of the disease (requiring prolonged antimicrobial treatment)⁸

The disease can be localized or disseminated with multiorgan involvement. Any organ can be involved in melioidosis with rapid development of small abscesses, which tend to coalesce to form larger abscesses, especially in lungs (50% of the cases), skin and subcutaneous tissues, bones and joints, liver, spleen, kidney, and brain. Most commonly, melioidosis presents as an acute pulmonary infection, causing fulminant necrotizing pneumonia, septicemia, and death, or as an indolent cavitary disease, and mild bronchitis.² Urogenital melioidosis, with prostate and kidney involvement, is a small proportion of all melioidosis cases and is more common in Northern Australia.⁹ Severe melioidosis is usually seen in immunocompromised patients (with poorly controlled diabetes mellitus or renal failure).⁵ Metastatic infection can remain latent for years. Common laboratory findings include anemia, neutrophilcytosis, coagulopathy, and renal and hepatic abnormalities.¹⁰

Cutaneous Manifestations

Very rarely, melioidosis can be demonstrated as a subacute form with cutaneous manifestations only.^{11–13} Skin involvement, seen in 10%–20% of the patients with melioidosis, varies greatly. Patients often have pustules and cutaneous abscesses, associated with lymphangitis, cellulitis, or regional lymphadenitis.^{10,14,15} Draining sinuses from lymph nodes or bone may develop. Abscesses may ulcerate¹⁶ and sometimes can form ecthyma gangrenosum-like lesions, or even progress to necrotizing fasciitis.^{10,17} The most common cutaneous manifestation in children is acute suppurative parotitis. Severe urticaria has been described in one case of pulmonary melioidosis.¹⁸ There are also some case reports of melioidosis, associated with cutaneous polyarteritis nodosa and porphyria cutanea tarda.^{19,20} In acute septicemia, patients may develop nonspecific flushing, cyanosis, and a pustular eruption.²¹

Differential Diagnosis

Due to the variety of skin presentations, many infectious diseases must be considered: fungal infections, tuberculosis, and atypical mycobacterial infections. Cat scratch disease, tularemia, and lymphogranuloma venereum have

similar clinical and histologic presentations. Staphylococcal and streptococcal infections should also be considered.

Treatment

The treatment of melioidosis includes intensive care, draining of abscesses, and antimicrobial therapy. Usually a *B. pseudomallei* antibiogram shows resistance to aminoglycosides, polymyxins, fluoroquinolones, and many beta-lactams (the older-generation penicillins and cephalosporins); nevertheless, the bacillus is highly susceptible to amoxicillin/clavulanic acid, tetracyclines, and chloramphenicol. The treatment of melioidosis requires multiple antimicrobial combinations. Resistance to a single antimicrobial may occur during the treatment. A course of antimicrobials is recommended for at least 2 months but may require prolonged antimicrobial therapy to prevent complications, including osteomyelitis, sepsis, and (rarely) rupture of a mycotic aneurysm.^{22,23} The localized cutaneous form of melioidosis can be successfully treated with combinations of amoxicillin/clavulanic acid (60 mg/kg/day orally three times daily) and tetracycline (40 mg/kg/day orally three times daily) or trimethoprim/sulfamethoxazole (co-trimoxazole). Oral co-trimoxazole is the agent of first choice for postexposure prophylaxis with duration of 21 days. In case of resistancy, the second-line choice is co-amoxiclav. Systemic involvement requires an extra use of intravenous (IV) ceftazidime (120 mg/kg/day twice daily) for 2–4 weeks, or meropenem reserved for severe cases (e.g., neuromelioidosis), plus the oral combination described above for the subclinical forms of melioidosis.^{16,24}

TYPHOID FEVER

Salmonella infections in humans include gastroenteritis, typhoid fever, bacteremia, and localized infection. Localized infection is a complication commonly affecting bones and joints, although subcutaneous, splenic,²⁴ breast, and intraperitoneal abscesses^{25–29} have been described. Typhoid fever is a systemic febrile disease caused by *Salmonella typhi*, a flagellated, gram-negative bacillus belonging to the Enterobacteriaceae family. The infection occurs most often during travel to endemic regions (with 18 times greater risk compared with the other), such as the Indian subcontinent, Southeast and Far-East Asia, the Middle East, Africa, and Central and South America.³⁰ Small endemics can occur sporadically as the result of food handlers who are carriers of *S. typhi*. Worldwide typhoid fever remains a health threat. Reported cases now are fewer than 500 per year.³¹ The case-fatality rate is reduced to 2% by using the appropriate antimicrobials and improvements in supportive care; nevertheless, in some developing countries, the case-fatality rate is higher—approximately 30%.³² *S. typhi* affects only humans during the ingestion of food or water contaminated with the feces of patients with active diseases, or people who are asymptomatic carriers. The incubation period ranges from 5 to 21 days.³³ The severity of disease is in parallel with the amount of bacteria ingested. The illness is usually characterized by nonspecific manifestations.

Clinical Features

Typhoid fever classically presents with prolonged fever, headache, paradoxical bradycardia, and gastrointestinal symptoms and signs, including abdominal pain³⁴ and a rose-colored eruption. Many extra intestinal manifestations of *S. typhi*

infection, such as osteomyelitis, intraabdominal abscess, urinary tract infection, and meningitis, have been described.³⁵ Fever, which is seen in 98%–100% of patients, is the most common finding. The classic relative bradycardia (Faget sign) and the presence of rose spots³⁶ are the clues to the diagnosis. Laboratory findings in this infection are also nonspecific: thrombocytopenia, proteinuria, elevated transaminases, and relative leukopenia.³⁷ Initially, patients present with diarrhea and abdominal pain. Other associated signs, less commonly found, are a nonproductive cough, constipation, meningismus, deafness, confusion, and weight loss. Asymptomatic hepatitis is common. Severe kidney and liver failure with marked jaundice has also been described. Pancreatitis can occur in typhoid fever, ranging from enzyme abnormalities to pancreatic abscesses requiring surgery.³⁸

Early diagnosis and treatment of typhoid fever allow prevention of the complications and spread of the infection. Complications may occur involving any organ and system. Splenic abscess represents nearly 30% of complicated *Salmonella* abdominal infection of untreated typhoid fever.^{34,39} Other complications are intestinal hemorrhage and perforation. Perforation classically occurs in Peyer patches of the terminal ileum. Other less common complications include toxic myocarditis, hepatitis, cholecystitis, polymyositis, mild bronchitis, and a toxic state of confusion.³⁷ Typhoid fever may affect the kidneys, leading to nephrotic syndrome.^{31,38} A chronic carrier state may occur in up to 3% of treated patients. Patients with cholelithiasis are at greater risk for persistence of *S. typhi*.

Cutaneous Manifestations

In 30%–50% of patients,³⁷ so-called rose spots are described as the cutaneous classic manifestation. The spots are caused by bacterial embolization, and bacterial cultures taken from the rose spots may be positive. Lesions are characterized as pink blanching papules, 2–4 mm in diameter, localized mainly on the mid-trunk, developing often between the 7th and 12th days of infection.

Subcutaneous abscesses may rarely occur as a localized skin and soft-tissue complication due to *S. typhi* bacteremia. *Salmonella* bacteremia increases in patients with acquired immune deficiency syndrome (AIDS), in whom these abscesses are found.⁴⁰ Abscess formations in most described cases are secondary and usually do not ulcerate. Most reported cases of subcutaneous abscesses have been due to *Salmonella* species other than *S. typhi*.^{39,40} A unique case of cutaneous ulceration occurred as a clinical manifestation of *S. typhi* infection in a nonimmunocompromised patient with complete absence of systemic signs.⁴¹ Another possible skin presentation is pustular dermatitis. Purpura or skin petechiae are rare and are described mainly in the setting of *Salmonella* endocarditis.³⁵ A patient with cutaneous leukocytoclastic vasculitis associated with abdominal lesions developed during typhoid fever but without endocarditis was reported.³⁹

Differential Diagnosis

The differential diagnosis of typhoid fever includes other systemic febrile illnesses: brucellosis, tularemia, leptospirosis, tuberculosis, rickettsial disease, viral hepatitis, mononucleosis, AIDS, and cytomegalovirus infection.³⁷ Additional infections to consider include malaria, dengue fever, and schistosomiasis. Noninfectious etiologies, such as lymphoma, leukemia, or an adverse drug reaction, can also cause prolonged fever.

Treatment

Antimicrobial therapy is necessary. Worldwide, chloramphenicol was the most commonly used antimicrobial for typhoid fever. Unfortunately, resistance to chloramphenicol has been increasing, especially in Southeast Asia. Amoxicillin and trimethoprim/sulfamethoxazole are also efficacious in the treatment of acute infection and the carrier state, but a high incidence of resistance is reported, too. Fluoroquinolones (e.g., oral ciprofloxacin 500 mg twice daily for 10 days) are currently the drugs of choice for typhoid fever, especially for infection with multidrug resistant (MDR) *S. typhi*.⁴² They have the lowest incidence of both relapse and development of a chronic carrier state; however, fluoroquinolone resistance and treatment failure of typhoid fever have been published.⁴³ MDR strains were considerably more prevalent in Iraq (83%) and Pakistan (52%), compared to the other countries.⁴⁴ The third-generation cephalosporins (e.g., IV ceftriaxone 2 g/d for 5 days, especially for patients with cholelithiasis) are also effective for treatment of typhoid fever.

LEPTOSPIROSIS

Leptospirosis is a spirochetal infection caused by pathogenic *Leptospira* species. The spirochetes have hooked ends, and due to this observation, Stimson named them *Spirochaeta interrogans* for their resemblance to a question mark.⁴⁵ Within the species of *Leptospira interrogans*, 200 serovars are recognized. Leptospirosis is presumed to be the most widespread zoonosis in the world,⁴⁶ with many wild and domestic animal reservoirs.

Leptospirosis causes clinical illness in both humans and animals. Human infection is typically due to exposure to infected animal urine, by direct contact or indirect exposure through water or soil.⁴⁷ The usual portal of entry is damaged skin or the conjunctiva. Inhalation of water or aerosols may result in infection of the respiratory tract.⁴⁸ Rarely, infection may follow animal bites.^{49,50} The incidence of infection is significantly higher in tropical countries ("honeymoon fever" of Western travelers) due to warm and humid conditions, allowing much longer survival of leptospires.^{51–53} The disease is seasonal, with peaks (in the summer) in temperate regions and (in rainy seasons) in areas with warm climates. Cases of leptospirosis also follow floods and hurricanes.^{54,55} Within the United States, the highest incidence was found in Hawaii.⁵⁶ Leptospirosis is highly endemic in Malaysia^{57,58} and Nicaragua.^{59–62} Some occupational groups have a significant risk for leptospirosis. The infection was recognized early on in sewer workers (first reported in the 1930s),^{63–66} then in fishworkers (86% of all cases in northeast Scotland) and coal miners.⁶⁷ More recently, fish farmers have been shown to be at higher risk,⁶⁸ particularly for infection with *L. icterohaemorrhagiae*,⁶⁹ due to the high mortality rate associated with the *L. icterohaemorrhagiae* serogroup.

Clinical Features

The spectrum of human leptospirosis is extremely wide, ranging from subclinical infection to severe multiorgan dysfunction with a high mortality rate. Leptospirosis involves nearly all organ systems, but mainly the liver and kidney. The classic syndrome of Weil disease represents only the most severe presentation. This syndrome, demonstrated by icteric leptospirosis with renal failure, was first reported by Adolf Weil in Heidelberg.⁷⁰

In humans, severe leptospirosis is frequently caused by serovars of the *L. icterohaemorrhagiae* serogroup. In Europe, serovars *L. icterohaemorrhagiae* and *L. copenhageni*, carried by rats, are usually responsible for leptospiral infection. The clinical manifestation of leptospirosis is biphasic, with an acute or septicemic phase lasting about a week, followed by the immune phase, characterized by antibody production and excretion of leptospires in the urine.^{71,72} Most of the complications of leptospirosis are associated with tissue invasion of leptospires during the immune phase of the infection. The majority of cases are subclinical and mild. A smaller proportion of anicteric leptospirosis presents as an afebrile illness, with chills, severe headache (with retroorbital pain and photophobia), myalgia, abdominal pain, conjunctival suffusion, and (rarely) a skin eruption. In addition, aseptic meningitis may be found in 25% of all cases.

There may also be an icteric form of the disease.⁷³ The mortality is almost nil in the anicteric form, but 2.4% of the anicteric patients in a Chinese outbreak developed massive pulmonary hemorrhage and death.⁷⁴ The icteric form of the disease affects between 5% and 10% of all patients with leptospirosis.⁷⁵ Icteric leptospirosis is more severe, often rapidly progressive, with a high mortality rate, and ranges between 5% and 15%. The jaundice occurring in leptospirosis is not associated with hepatocellular necrosis. Serum bilirubin, transaminase, and alkaline phosphatase level elevations are usually minor. Leptospirosis is a common cause of acute renal failure (ARF), which occurs in 16%–40% of cases.^{76–78} Serum amylase level is often significantly increased in association with ARF,^{79,80} but clinical signs of pancreatitis are rare. Thrombocytopenia occurs in more than 50% of cases, is usually associated with multiorgan involvement, and is a predictor for ARF development.^{81,82}

Thrombocytopenia in leptospirosis is transient and does not result from disseminated intravascular coagulation.^{83,84} Pulmonary involvement can be the major manifestation of leptospirosis in some cases.^{85–87} The severity of respiratory disease is unrelated to the presence of jaundice.⁸⁸ Pulmonary signs and symptoms may present with cough, dyspnea, hemoptysis (from mild to severe), and adult respiratory distress syndrome. Intraalveolar hemorrhage may be found, even in the absence of pulmonary symptoms, and may be severe, causing death.^{89–91} Radiographic abnormalities are most commonly noted in the first week of the disease, presented by alveolar infiltrates. Cardiac involvement is a frequent complication of leptospirosis, although significant left ventricular dysfunction is rare.

Cutaneous and Mucosal Manifestations

The skin eruption in the anicteric form of leptospirosis is often transient, lasting less than 24 hours. Petechial, ecchymotic, or purpuric skin lesions may occur in leptospirosis. Conjunctival suffusion is seen in the majority of patients and in the presence of scleral icterus, which is thought to be pathognomonic for Weil disease.⁹² Bacterial causes of erythema nodosum, in particular leptospirosis, also should be considered.⁹³ A rare complication of leptospirosis may be Kawasaki syndrome.^{94,95} and a patient with anicteric leptospirosis has presented with respiratory insufficiency and acquired ichthyosis.⁹⁶ The sudden appearance of ichthyosis, especially in adults, has been considered a marker of systemic disease. Acquired ichthyosis may be associated with malignant disease and autoimmune disorders, as well as systemic infections (i.e., the association of leptospirosis and ichthyosis mentioned earlier in this chapter).

Differential Diagnosis

The multiorgan involvement of leptospirosis may be confused with other tropical infections: malaria, dengue, enteric fever, typhoid fever, and melioidosis. Influenza should be considered in mild anicteric cases.

Treatment

Therapy varies depending on the duration and severity of the symptoms and signs. Patients with mild, flu-like symptoms are treated only symptomatically. The management of icteric leptospirosis requires admission and treatment of the patients in an intensive care unit. Patients with ARF need dialysis. Cardiac monitoring is also necessary during the first few days.

The antimicrobial susceptibility of 13 *Leptospira* isolates (from Egypt, Thailand, Nicaragua, and Hawaii) to 13 antimicrobial agents has been studied. Leptospire were susceptible to penicillin G, cefotaxime, ceftriaxone, and fluoroquinolones (moxifloxacin, ciprofloxacin, and levofloxacin). Tetracyclines had the highest MIC90s (minimum inhibitory concentration required to inhibit the growth of 90% of organisms).⁹⁷ Leptospiral infection can be successfully treated with penicillin G, third-generation cephalosporins, or doxycycline.⁹⁸ IV penicillin should be given at a dosage of 8 million units/day for 7–10 days.^{99,100} A treatment regimen of oral doxycycline is 100 mg twice daily; for short-term prophylaxis—doxycycline 200 mg once weekly.¹⁰¹

PLAGUE

Plague is a synonym of an old and forgotten infection, often used today with a totally different meaning: as a curse, trouble, or harassment. Globally, the World Health Organization reports 1000–3000 cases of plague naturally occurring worldwide every year. In 2006, a total of 13 human plague cases were reported in the United States. This is the largest number of cases reported in a single year in the United States since 1994.¹⁰²

The discovery of *Yersinia pestis* is a fascinating story. The microbe causing the disease was unknown until 1894, when Alexandre Yersin (1863–1943) described it. Yersin had been sent to Hong Kong to conduct research on a bubonic plague epidemic that was sweeping through China. Yersin arrived in Hong Kong on June 15, 1894. Seven days later, he observed that

fleas drink the rodent's blood, allowing *Y. pestis* to multiply in the flea's gut. The flea then regurgitates blood into the bitten area, infecting the subject. Rodents or humans then carry *Y. pestis* in their blood.

Working in a small bacteriologic research laboratory set up for him, he isolated the plague bacillus. The Japanese bacteriologist Shibasaburo Kitasato (1852–1931) had arrived shortly before Yersin in Hong Kong. Within a few days, he also found a bacillus and telegraphed his findings to the world. Kitasato published his findings in Japanese and English at the same time that Yersin published his discovery in French. People in various parts of the world credited one or the other with the discovery, depending on which journals they had read. Yersin named the organism *Pasteurella pestis* after his teacher Louis Pasteur (1822–1895), but since 1970, the bacillus has been known as *Yersinia pestis*. Plague is an infectious disease of animals and humans caused by the bacterium *Y. pestis*. *Y. pestis* is a non-spore-forming, gram-negative coccobacillus measuring $1.5 \times 0.75 \mu\text{m}$. The genome of *Y. pestis* has been sequenced, including the three virulence plasmids, pPst, pLcr, and pFra.¹⁰³ *Y. pestis* belongs to the group of bacilli with low resistance to environmental factors. Sunlight, high temperatures, and desiccation have a destructive effect, and ordinary disinfectants, such as Lysol and preparations containing chlorine kill it in 1–10 minutes. *Y. pestis* circulates, particularly in rodents, in the natural foci of infection found on all continents except Australia.

Plague is spread from one rodent to another by flea ectoparasites and to humans either by the bite of infected fleas or when handling infected hosts (Figure 25.1). At least 30 types of fleas and more than 200 species of mammals in 73 genera serve as reservoirs.¹⁰⁴ Plague has had three pandemic waves¹⁰⁵:

- The first certain plague pandemic, known as Justinian's plague, was recorded in the sixth century CE. The epidemic spread over Asia, Africa, and Europe and claimed nearly 100 million victims.
- The second plague pandemic is the well-known "Black Death" of the fourteenth century. It caused 50 million deaths, half of them in Asia and Africa and the other half in Europe, where a quarter of the population succumbed.
- The third plague pandemic began in Canton and Hong Kong in 1894. It was carried by rats aboard the steamships and spread rapidly throughout the world. Plague entered

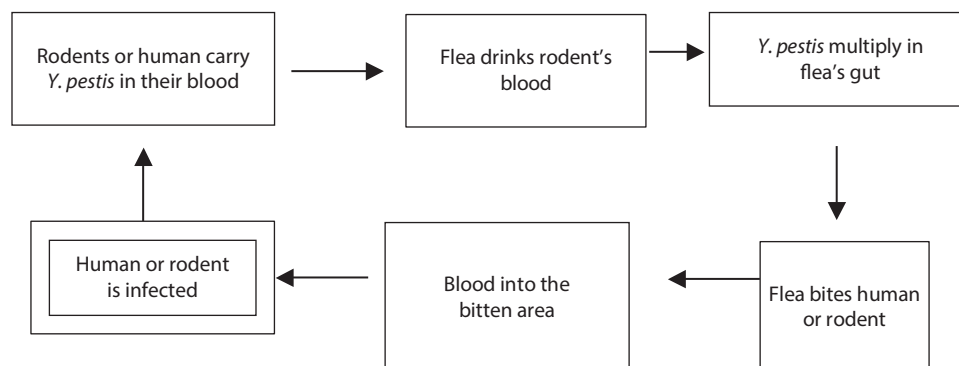


Figure 25.1 Usual pathway of plague transmission.

77 ports on five continents. The last great outbreak of plague occurred in the early 1900s in India, killing more than 20 million people.

There is a well-known classification of the clinical presentation of plague. Three types of plague are differentiated—bubonic, pneumonic, and septicemic:

- **Bubonic Plague.** The classic form of infection is the bubonic plague (Greek *boubon* = groin). It is transmitted only by a flea bite and is not spread from person to person. The incubation period varies from 1 to 8 days.
 - **Clinical Features:** The illness begins with fever, chills, and pain in the area of the lymph nodes.
 - **Cutaneous Manifestations:** The characteristic sign is the painful, swollen, and warm to the touch lymph node (a “bubo”), which occurs in the groin, axilla, and/or cervical region. The bubo location is primarily a function of the region of the body in which an infected flea inoculates the plague bacillus. Buboes are usually 1–10 cm in diameter and may suppurate and rupture. Nausea, vomiting, and/or diarrhea are common as systemic manifestations of the infection. This form may progress to secondary pneumonic plague or secondary septicemic plague. Bubonic plague has a 1%–15% death rate in treated cases and a 40%–60% death rate if left untreated.
 - **Differential Diagnosis:** A wide differential diagnosis could be made with cat scratch disease, ulceroglandular tularemia, staphylococcal or streptococcal adenitis, mycobacterial infection, lymphogranuloma venereum, chancroid, primary genital herpes, and even a strangulated inguinal hernia.
- **Pneumonic Plague.** Pneumonic plague is the deadliest form. It is caused by inhaling the bacteria and transmitting it. The transmission requires close contact with an infected person. The incubation period is up to 6 days.
 - **Clinical Features:** Pneumonic plague begins with a fulminant fever, malaise, myalgias, headache, and gastrointestinal symptoms. The death rate from pneumonic plague is 100% if not treated within the first 24 hours of infection.
 - **Cutaneous Manifestations:** Patients in the terminal stages often develop large ecchymoses on the back: “the Black Death.”
 - **Differential Diagnosis:** The differential diagnosis includes any case of severe gram-negative pneumonia, community-acquired pneumonia (bacterial, *Mycoplasma*, *Legionella*, *Chlamydia*), viral pneumonia (influenza, respiratory syncytial virus, cytomegalovirus, hantavirus), Q fever, inhalational anthrax, tularemia, or ricin poisoning. An outbreak of pneumonic plague has appeared in a remote diamond mine in the Democratic Republic of the Congo. The multidisciplinary team of epidemiologists, physicians, and logisticians from Médecins Sans Frontières confirmed 136 cases of pneumonic plague, 57 of them fatal.¹⁰⁶
- **Septicemic Plague.** Septicemic plague is caused by flea bites or is a result of bubonic or pneumonic plague. It is not spread from person to person and occurs when plague bacteria multiply in the blood. In this form, lymph nodes usually do not enlarge. It is not contagious and has a 40% death rate in treated cases and 100% in untreated cases.
 - **Clinical Features:** The clinical picture includes acute fever, chills, prostration, abdominal pain, nausea, vomiting, and internal bleeding.
 - **Cutaneous Manifestations:** Purpuric skin lesions and gangrene of the distal digits (acral necrosis) are common. Rose-colored purpuric lesions give rise to the nursery rhyme, “Ring around the rosy.”¹⁰⁷
 - In all forms, skin lesions may occur at the site of flea bite (papules, vesicles, pustules), and petechiae and ecchymoses may occur during hematogenous spread. Ecthyma gangrenosum has been reported in several patients as a rare skin sign.¹⁰⁸
 - **Differential Diagnosis:** Differential diagnosis should be made with gram-negative sepsis, meningococemia, rickettsiosis, malaria, and appendicitis.
 - **Laboratory:** There are no widely available, rapid diagnostic tests for plague. Blood, bubo aspirates, and sputum should be stained with Giemsa stain. Smears typically show the bacillus to have a bipolar or “safety pin” appearance. *Y. pestis* is slow growing on blood cultures, bubo aspirate, sputum, or skin lesions. Direct fluorescent antibody testing for *Y. pestis* capsular (F1) antigen may be helpful.
 - Several serologic tests are also available (passive hemagglutination, enzyme-linked immunosorbent assay). A single titer of more than 1:10 is positive for plague if the patient has not been vaccinated previously. With paired sera 4–6 weeks apart, a fourfold increase in titer is considered confirmatory.

Treatment

The patients require isolation. The preferred therapy is streptomycin (1 g intramuscularly [IM], 12 h), or gentamicin (5 mg/kg IM or IV once daily, or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV). Alternative therapeutic regimens are courses with doxycycline (100 mg every 12 h or 200 mg once per day), ciprofloxacin (400 mg every 12 h), or chloramphenicol (25 mg/kg every 6 h, max 4 g/d for 10 days). In pregnant women, gentamicin is the preferred choice.

As prevention, close physical contact is restricted to proximity of no less than 2 m to a person who is symptomatic with plague. All health-care personnel must take precautions—wear goggles, gloves, gowns, and masks. In endemic areas, personal protective measures, such as the use of insecticides and insect repellents, are recommended for reducing the incidence of infection.¹⁰⁹

Commercial plague vaccines were developed as early as 1896, when killed bacteria were first used by Greer Laboratories (Lenoir, North Carolina) in its production. Nowadays, no vaccines are currently in production. Plague may be rare today, but health-care personnel should be reminded about the characteristic clinical signs of this infection, because the bacillus is easily aerosolized and the clinical manifestations are not likely to arouse suspicion until an epidemic is evident. Its potential use as a bioweapon should not be overlooked.¹¹⁰

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Skin signs of systemic neoplastic diseases and paraneoplastic cutaneous syndromes

Kyrill Pramatarov

The skin may reflect many visceral diseases, malignancies included. Sometimes, the skin may even give a clue to the underlying neoplasm. The Swiss dermatologist Delacrétaz has defined the term “paraneoplasia”:

Cutaneous paraneoplastic syndromes are non-metastatic manifestations on the skin as a result of the existence of a malignant visceral tumor and/or disease of the lymphoma group, especially leukaemias. The close relation between the dermatosis and tumor is confirmed by the phenomenon of disappearance or not at all influenced skin disease, if the malignant tumor is eliminated by operation, irradiation or cytostatics. The recurrence of the skin changes (dermatosis) indicates a relapse of the tumor or metastases.¹

The paraneoplastic signs or syndromes may precede, appear parallel to, or follow the appearance of the internal malignancy. There are many classifications of the paraneoplastic signs and syndromes, utilizing a variety of criteria. Some of them are based on the morphology of skin changes, while others are based on the frequency of the association of dermatosis/visceral malignancy. The paraneoplastic signs and syndromes may be divided into two groups: indirect associations and direct associations with parallel evolutions corresponding to the paraneoplastic syndrome. The pathogenesis of the development of paraneoplasias includes

- Peptides, mediators, and hormones released from the tumor
- Immunologic defense reactions induced by the tumor antigens and appearing after cross-reaction with the structures of the skin
- Deposits of immunocomplexes of tumor antigens and antibodies²
- Various cytokines and possibly growth factors³

Metastases to the skin are more specific signs of internal cancer. Sister Mary Joseph nodule (Figure 26.1) may be considered more as metastases from an intraabdominal malignancy. Clinically, the Sister Mary Joseph nodule is an indurate nodule or plaque. The surface of the nodule is sometimes ulcerated with exudation of purulent or mucosal discharge. Occasionally, the lesions form a tumor. Sister Mary Joseph nodules are signs of an advanced intraabdominal malignancy. They appear as a sign of previously diagnosed neoplasia. The primary malignancy is localized in the gastrointestinal or genital tract, mainly as gastric adenocarcinoma, but also as adenocarcinoma of the ovary, colon, pancreas, prostate, or liver.⁴

DERMATOSES HIGHLY ASSOCIATED WITH MALIGNANCY

Acanthosis Nigricans Maligna

Besides malignant acanthosis nigricans, there is a benign form that may develop under various circumstances—endocrinopathy and drug-induced forms. It may also be a clinical presentation of congenital conditions.

In the malignant form, some epidermal growth factors produced by the tumor cells are responsible for the clinical appearance. Clinically, malignant acanthosis nigricans is characterized by brown verrucous plaques. They are located symmetrically on the nape, groin, and axillae. Similar lesions, but mostly darkly pigmented papules, appear on the lips, eyelids, nipples, and anogenital area.

There is an extreme form that is always a clinical sign of an internal malignancy. Brown thickening of the skin over the dorsa of fingers or the palms may also occur. Oral lesions may be present, as well. Malignant acanthosis nigricans is associated with adenocarcinoma of the gastrointestinal tract, cancer of the lung, gynecologic tumors, and lymphomas.^{5,6}

Bazex Syndrome

Bazex syndrome (acrokeratosis paraneoplastica) is usually associated with carcinoma of the upper digestive tract, including neoplasms of the lower lip, tongue, tonsils, esophagus, and pharyngolaryngeal region (Figure 26.2). The upper part of the respiratory tract (the upper third of the lung, especially) also may be involved with malignancy in this syndrome. Other tumors have been reported, as well: cancer of the prostate, bladder, and lower part of the leg, and some hematologic malignancies. The skin lesions appear in several phases. Initially, they may resemble dermatitis, psoriasis, or lupus erythematosus. They begin with erythema and scaling and appear on the fingers and toes. Rarely, vesicles, bullae, and crusts are present. The lesions are not itchy or painful. The nails are hypertrophic with onycholysis. Sometimes, paronychia is present. Similar changes appear on the nose and conchae of the ears. In the later stages of the disease, the skin of the trunk is also involved. Pityriasiform scaling appears on the surfaces of the hands and feet. This scaling and a livid erythema appear on the skin of the arms, legs, and trunk, and (in severe cases) an erythroderma may be present. The skin changes may even become hyperkeratotic on the skin of the hands and feet.⁷⁻¹⁰

Erythema Gyrratum Repens

Erythema gyratum repens is a paraneoplastic syndrome of unknown etiology. The lesions of this syndrome consist of erythematous concentric rings that form the classic wood-grain



Figure 26.1 Sister Mary Joseph nodule.



Figure 26.2 Bazex syndrome. (Courtesy of V Benea, MD.)



Figure 26.3 Erythema gyratum repens.

appearance (Figure 26.3). They may be flat or raised. The skin changes are localized on the trunk, arms, and thighs and proximal aspects of the extremities. The feet, hands, and face are usually not affected. The rings spread outward in a serpiginous pattern. The lesions are itchy, and the pruritus may be severe.^{11,12}

The pathogenesis is still obscure. Immunologic pathogenesis of erythema gyratum repens is possible, because granular deposits of immunoglobulin G and C3 have been detected at the basement membrane zone of both involved and uninvolved skin.¹³ In 82% of erythema gyratum repens patients, there is an internal malignancy of the lung, breast, stomach, and/or esophagus. Regression of the skin lesions usually occurs with treatment of the underlying cancer. Other diseases,

such as tuberculosis, CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome, and sclerodactyly, also have been reported in association with erythema gyratum repens.¹⁴

Muir-Torre Syndrome

Muir-Torre syndrome is a rare autosomal dominant disorder. The skin lesions of Muir-Torre syndrome consist of sebaceous epithelioma, adenoma, or carcinoma and multiple keratoacanthomas. The skin changes may precede the appearance of the internal malignancies, but more often they occur later. The internal malignancies are multiple. They are less aggressive, and metastases rarely occur. The tumors are mostly colorectal cancers. In 50% of patients, tumors of the

genitourinary tract, breast, and/or upper gastrointestinal tract are detected.^{15,16}

The Sign of Leser-Trélat

The sign of Leser-Trélat presents with numerous seborrheic keratoses, known as seborrheic warts or verrucae senilis. They are common in elderly people, but the sign of Leser-Trélat must be considered as a paraneoplastic sign, if there is a sudden increase in the number or size of previous existing keratoses and if their appearance is associated with an internal malignancy.¹⁷ The lesions are itchy. Association of the sign of Leser-Trélat with malignant acanthosis nigricans is quite possible, and this association supports the hypothesis of the paraneoplastic nature of the sign. There are no histologic differences between common seborrheic keratosis and those with malignancy.

The pathogenesis of the sign is unclear. Probably, a tumor-secreted growth factor plays a role in its appearance. In most patients with the sign of Leser-Trélat, adenocarcinoma of the stomach is detected. The reported cases with the sign of Leser-Trélat had malignancy of the breast, colon, and/or rectum; less frequently, they had cancer of the duodenum, esophagus, pancreas, ovary, uterus, cervix, prostate, and/or gallbladder. The associated malignant diseases have an aggressive course; thus, the sign of Leser-Trélat is a poor prognostic sign. Association of the sign of Leser-Trélat has been reported with many hematologic disorders, such as mycosis fungoides, lymphoma, leukemia, and melanoma.^{18,19}

Necrolytic Migratory Erythema (Glucagonoma Syndrome)

Necrolytic migratory erythema (glucagonoma syndrome) is strongly associated with the glucagon-secreting pancreatic islet cell tumor. Skin changes are erythematous, scaly, and then crusted. Blisters can appear after pustular evolution due to bacterial or mycotic superinfection. The lesions are often confluent and painful. The skin changes are localized on sites of friction and pressure, such as feet and legs, but also on buttocks, groin, and the pubic area. Additionally, mucocutaneous lesions such as atrophic glossitis, cheilitis, stomatitis, balanoposthitis, or vulvovaginitis can appear. Because the condition is associated with pancreatic tumors, high blood sugar levels are expected. The erythrocyte sedimentation rate is high. The amounts of free amino acids and of free fatty acids are low.^{20,21}

Sweet Syndrome

Sweet syndrome (acute febrile neutrophilic dermatosis) can occur without other pathologic processes, but most commonly it might be associated with malignancy (Figure 26.4). In 85% of cases, malignancy-associated Sweet syndrome is a marker of hematologic neoplasm. The hematologic malignancies include acute myeloid leukemia, Hodgkin disease, non-Hodgkin lymphoma, myelodysplastic syndrome, myeloproliferative disease, and chronic myelogenous leukemia. The idiopathic form presents with tender plaques or nodules located on the face, hands, and/or upper extremities. The skin is erythematous and livid. Diameters of the lesions vary. Fever accompanies the skin changes, and neutrophilia is detected. The condition responds promptly to corticosteroids. There is a difference in the skin signs between the idiopathic and



Figure 26.4 Sweet syndrome.

malignancy-related forms. The latter are more severe, vesicular, bullous, or ulcerative. Other dermatoses can appear in the malignancy-related variant, such as pyoderma gangrenosum, erythema nodosum, or erythema multiforme. In the paraneoplastic form, the mucous membranes can be affected as well. The extracutaneous involvement is more frequent: musculoskeletal signs and symptoms, involvement of the eyes, and glomerulonephritis. In the paraneoplastic variant, there is absence of neutrophilia, which is common in the idiopathic form.^{22,23}

Other Genodermatoses

Besides Muir-Torre syndrome, there are several autosomal dominant tumor-associated genodermatoses. These include Gardner syndrome, Peutz-Jeghers syndrome, and Cowden syndrome. In Gardner syndrome, multiple epidermoid cysts, fibromas, and primary osteoma of the skin (which are associated with cancer of the colon) are present.²⁴ In Peutz-Jeghers syndrome, multiple perioral and mucosal lentigines are observed. The skin changes are present beginning in early childhood, but later the patients develop tumor of the testis, ovaries, pancreas, and/or gastrointestinal tract.²⁵ In Cowden syndrome, multiple trichilemmomas, trichoepitheliomas, hemangiomas, and oral and acral papules appear in association with breast and thyroid cancer or tumors of the gastrointestinal tract.²⁶

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is a mucocutaneous blistering disease associated with malignancy and caused by Hodgkin disease, non-Hodgkin lymphoma, chronic lymphocytic leukemia, and/or Castleman disease, as well as Waldenstrom macroglobulinemia, T-cell lymphoma, thymoma, retroperitoneal sarcoma, and/or reticulum cell sarcoma. Reports on association with solid cancers are isolated.^{27,28}

DERMATOLOGY DISORDERS THAT MAY BE ASSOCIATED WITH MALIGNANCY

Pyoderma Gangrenosum

Pyoderma gangrenosum begins as a papule or pustule that later develops into an erythematous nodule. These nodules form an ulcer with irregular borders. The lesions have a necrotic base, and hemorrhagic exudates may be present. The lesions are painful and have a predilection for lower extremity involvement. The sign of pathergy is present, and lesions develop after minor trauma.²⁹

Pyoderma gangrenosum is associated in approximately 50% of patients with such systemic diseases as ulcerative colitis, Crohn disease, and inflammatory arthritis.³⁰ In 7% of cases, hematologic malignancies, most commonly leukemias and multiple myeloma, are detected.²⁹ When the condition is associated with hematologic disorders, bullae may also be seen on the face.³¹ Pyoderma gangrenosum may be associated with cancer of the colon, prostate, breast, and bronchus.³²

Dermatomyositis

Dermatomyositis is an inflammatory myopathy with characteristic skin manifestations. The diagnostic criteria of dermatomyositis include symmetrical proximal muscle weakness, inflammatory myopathy, elevation of serum levels of muscle enzymes, electromyographic evidence of myopathy, and

typical cutaneous findings of dermatomyositis. The prevalence of malignancy in dermatomyositis ranges from 3% to 60%.³³ Dermatomyositis may precede, occur concurrently with, or develop after the malignancy. The most expected tumors associated with dermatomyositis are cancers of the ovary, stomach, lung, and/or breast.^{34,35}

Clubbing

Digital clubbing is associated not only with a disabling lung disease, mostly pulmonary emphysema, but also with chronic bronchitis, hepatic cirrhosis, and inflammatory intestinal diseases. It is characterized by an increase in the diameter of the distal phalanges and alterations to the fingernails. The disorder is classified into five phases. It begins with an increase and fluctuation of the ungual bed and, in the last phase, increase of the extremity with thickening of the distal phalange and longitudinal striations are observed.³⁶ Digital clubbing is associated with bronchogenic cancer, and in this paraneoplastic form, the bones are not usually changed.³⁷

Tripe Palms

Tripe palms present with brown thickening of the skin of the palms, resembling pig intestine; hence, the name. The epidermal ridges are broadened, and the sulci are deep. These changes are associated with internal malignancy and usually appear with acanthosis nigricans.³⁸

Hypertrichosis Lanuginosa

This paraneoplastic sign occurs in women, mostly. The face is mainly affected. Less frequently, hypertrichosis is observed on the neck, trunk, arms, and legs. It must be differentiated from hirsutism and hypertrichosis, which occur due to androgens produced by some endocrinologic disorders.

Table 26.1 Dermatologic Diseases and Disorders in Association with Malignancies

Skin disorder	Related malignancy	References
Porphyria cutanea tarda	Hepatocellular carcinoma	Federman et al. ⁴¹
Amyloidosis	Multiple myeloma	Zappasodi et al. ²⁹
Ichthyosis acquisita	Multiple myeloma, non-Hodgkin lymphoma, Hodgkin disease	Zappasodi et al. ²⁹
Granuloma annulare	Non-Hodgkin lymphoma, Hodgkin disease, solid tumors	Cohen ⁴²
Sarcoidosis	Solid tumors of cervix, liver, lung, uterus, testicles, melanoma; leukemias, lymphomas, myeloma	Cohen ⁴²
Papuloerythroderma of Ofuji	T-cell lymphomas, hepatocellular carcinoma	Schepers et al. ⁴³ , Nishijima ⁴⁴
Bullous pemphigoid	Non-Hodgkin lymphoma	Zappasodi et al. ²⁹
Relapsing polychondritis	Adenocarcinoma of bladder, breast, bronchus, colon, lung, pancreas, prostate, rectum, vocal cords; leukemias, lymphomas, myeloma	Cohen ⁴²
Systemic lupus erythematosus	Solid tumors of breast, cervix, ovary, brain, colon, biliary tract, kidney, pancreas, stomach, rectum, thymus, urinary bladder; leukemias, lymphomas, myeloma, nonmelanoma skin cancer	Cohen ⁴²
Erythromelalgia	Myeloproliferative disease	Zappasodi et al. ²⁹
Subcorneal pustular dermatosis	Multiple myeloma, non-Hodgkin lymphoma	Zappasodi et al. ²⁹
Dermatitis herpetiformis	Non-Hodgkin lymphoma	Zappasodi et al. ²⁹
Linear immunoglobulin A dermatosis	Multiple myeloma, non-Hodgkin lymphoma	Zappasodi et al. ²⁹
Erythroderma and exfoliative dermatitis	Hodgkin disease, non-Hodgkin lymphoma	Zappasodi et al. ²⁹
Pityriasis lichenoides et varioliformis acuta	Mycosis fungoides	Kempf et al. ⁴⁵
Eosinophilic fasciitis	T-cell malignant neoplasm	Chan et al. ⁴⁶
Scleroderma	Ovarian cancer	Vottery et al. ⁴⁷
Pityriasis lichenoides chronica	Oncocytoma renis	Lazarov et al. ⁴⁸

Hypertrichosis lanuginosa appears with cancer of the lung and/or colon.³⁹

The vasculitides, which are a heterogenous group of diseases, are associated with cancer in approximately 5% of the patients. Most commonly, patients with paraneoplastic vasculitis have such hematologic malignancies as hairy cell leukemia and lymphomas. Vasculitis reported in association with hematologic malignancies includes leukocytoclastic vasculitis and polyarteritis nodosa.^{29,40}

OTHER DERMATOLOGIC DISEASES ASSOCIATED WITH MALIGNANCIES

Numerous additional dermatologic diseases and disorders have been reported in associations of malignancy (Table 26.1).

Additionally, dermatographism and pruritus must be considered as common paraneoplastic signs without any particular associations with malignancies.

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Burn injury

Samuel H. Allen and Remo Papini

Acute burns produce some of the most harrowing injuries encountered by persons working in the emergency and health-care services. These injuries have a high mortality and, should the patients survive, they will carry with them the lifelong scars—physical, psychologic, and emotional.

Worldwide, injury caused by fire is a major cause of morbidity, especially in sub-Saharan Africa, where open fires are used to heat food and water. Burns are among the leading causes of disability-adjusted life-years (DALYs) lost in low- and middle-income countries. Sadly, most of these injuries occur in toddlers.¹

In the developed world, house fires and industrial accidents are the major culprits causing burn injury. Some of the worst injuries are those that are self-inflicted.

In the United States alone, more than 500,000 people are seen in emergency departments each year as a result of burn injury; more than 50,000 are admitted to hospital; and more than 5000 deaths per year are attributed to the burn injury.

Approximately 50% of household and domestic burn injuries result from hot-water scalding and fires that occur in the kitchen. Most are managed outside hospital practice. Of the 250,000 burn injuries occurring per year in the United Kingdom, only 175,000 present to hospital, and only 16,100 are admitted for treatment. The highest rates of burn-related injury and death are observed in children younger than 5 years and elderly persons older than 75 years.² Since the introduction of gas-fired central heating and the tightening of health and safety laws, the incidence of these events has become less commonplace.

Heat energy is transmitted through radiation, conduction, and convection. Thermal injury usually occurs as a result of fire, but chemicals, electricity, and radiation can also cause burn injury. It is the direct effect of the flames' heat that causes the greatest harm. When the skin's integument is destroyed, the essential functions of the skin are lost, leading to profound fluid loss, heat loss, and infection, as well as inflammation and pain. To compound the injury, the burn is often associated with other injuries arising from the accident such as shock, smoke and debris inhalation, and blunt trauma such as may occur following an explosion. Superheated air may cause direct thermal injury leading to upper airway edema and obstruction of the respiratory tract. More than 50% of fire-related deaths are the result of smoke inhalation.

PATHOPHYSIOLOGY

A burn is caused by the coagulative destruction of the skin and mucous membranes, leading to blistering and local inflammatory changes. Larger injuries (over 25% total body surface area) are associated with systemic shock and organ hypoperfusion

that is compounded by the pathological fluid loss. After resuscitation, the patient attains a hypermetabolic state associated with gluconeogenesis, insulin resistance, and increased protein catabolism. Late complications can arise from tissue edema and swelling, which in turn may lead to compartment syndrome, superimposed infection, and contractures. Wound infection is often associated with multidrug resistant organisms as a result of prior use of broad-spectrum antibiotics. Psychologic sequelae are common and include posttraumatic stress disorder, depression, and body image disorder.

CLINICAL AND LABORATORY AIDS REQUIRED FOR DIAGNOSIS

In most cases of burn injury, the diagnosis and etiology are self-evident. Even so, it is essential to try to establish the time of the injury, as this will have implications in the management and anticipation of complications. What may be less clear at the time of the accident is the extent—and depth—of the injury.

Extent of Burn

A rapid and usefully accurate estimate of the body surface area of the injury can be calculated using the Rule of Nines (Figure 27.1).³

Calculation of body surface area differs in children. For children younger than 1 year, the head surface area represents approximately 18% of total surface area and the legs 14%; therefore, for children older than 1 year, one should add 0.5% to the leg area and subtract 1% from the head surface area for each additional year until adult values are attained. Alternatively, the Lund and Browder⁴ chart can be used to estimate body surface area in children. For a wide age range, the area of the palm plus palmar aspect of the digits represents 1% of the total body area.

Depth of Burn

Accurate assessment of the burn depth is important in making decisions about dressings and timing of surgery. The depth may not always be clear from the initial assessment.

Depth of burn was previously classified as first-, second-, or third-degree burn, but is now more accurately described as an epidermal, superficial, or deep partial-thickness or full-thickness burn (Figures 27.4 and 27.5).⁵

Epidermal Burns

By definition, these burns affect only the epidermis. The lesion is typified by sunburn. Erythema and pain are present. Blistering is unusual in this type of injury. The skin adnexa that

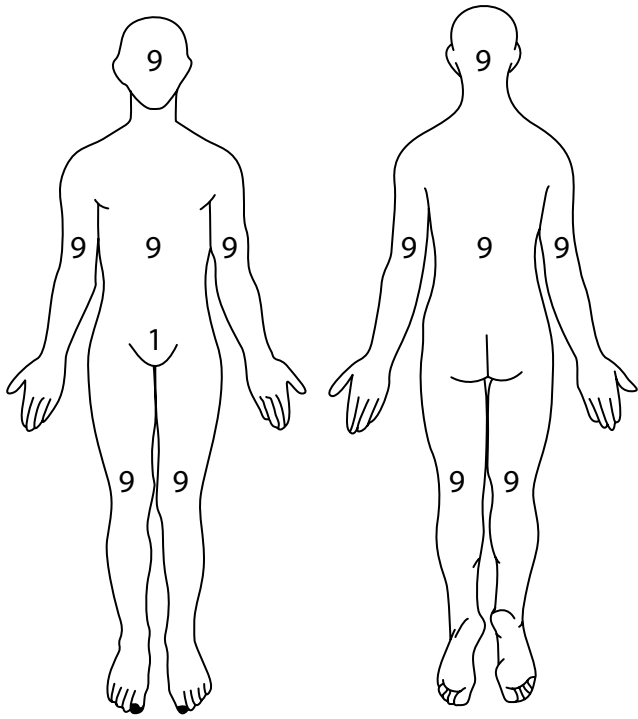


Figure 27.1 Rule of Nines. (Wallace AB. *Lancet* 1951;i:501–504.)



Figure 27.2 Superficial scald.

contain regenerating keratinocytes within the sweat glands and hair follicles are preserved, so the lesion normally heals within a week without scarring. Supportive therapy is all that is required. Regular analgesia and intravenous fluids may be required if there is extensive injury and/or signs of heat stroke.

Superficial Partial-Thickness Burns

These burns affect the superficial dermis (papillary layer) and epidermis. The lesion has a red or mottled appearance with



Figure 27.3 Deep dermal scald injury.

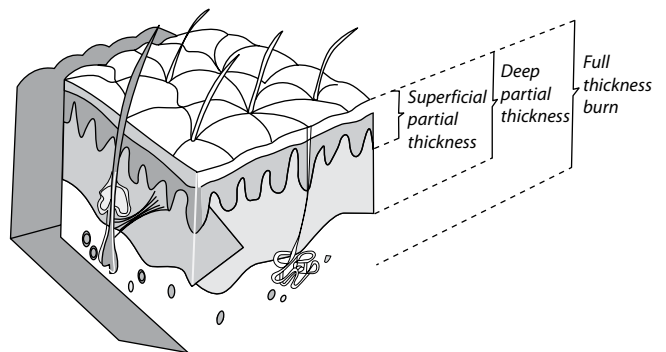


Figure 27.4 Classification of injury according to depth of burn.



Figure 27.5 Full-thickness flame burn (70% total body surface area).

associated swelling and blister formation. Scalding typically causes this type of lesion (Figures 27.2 and 27.3). The skin often has a weeping or wet appearance and may be hypersensitive, even to air. Exposure of the superficial nerves makes these injuries extremely painful. Healing is usually complete within 2 weeks depending on the density of skin adnexa. Thin hairless skin (e.g., inner arm and eyelids) will heal more slowly than thick or hairy skin (e.g., scalp or face), because it contains fewer hair follicles or sweat glands that contain the regenerating keratinocytes.

Deep Partial-Thickness Burns

Damage to the deep dermis, which is the reticular layer containing the superficial parts of the hair follicles and sweat and sebaceous glands, is often the most difficult to assess and treat. Initial lesions may appear superficial, even with blanching on pressure, but on reexamination 48 hours later show fixed capillary staining. Fewer skin adnexa—hence, islands of regeneration—are present at this depth, so healing is slower. The exposed dermis is pale white-yellow and insensate, because sensory nerves in the dermis are destroyed. Blistering is common, and there is no capillary refill. Lesions heal with scarring. If injuries are extensive or in functional or cosmetically sensitive areas, they are better excised to a viable depth and then skin-grafted for best functional recovery. Healing takes between 3 and 8 weeks.

Full-Thickness Burns

In full-thickness burns, all regenerative tissues are destroyed such that healing may only naturally occur from the edges of the wound. Consequently, healing usually results in considerable contraction. The skin may vary in appearance between appearing dark, charred, and leathery to appearing translucent, mottled, or waxy white. Occasionally, the injury may be missed, being mistaken for unburnt skin. All full-thickness burn injuries should be excised and grafted unless they are small (<1 cm in diameter) or in an area that would not compromise function. Analgesia to pinprick signifies a deep dermal or full-thickness injury.

The clinical features of epidermal and partial- and full-thickness burns are shown in Table 27.1. A so-called fourth-degree burn exhibits destruction of the subcutaneous fat, muscle, and sometimes bone. Such injury requires major reconstruction and often amputation.

THERAPY

The chances of surviving a complex major burn injury are better now than ever before. Patients should be managed on a specialized burn unit or center with experience in managing these

types of injury. This management usually involves a multidisciplinary effort involving the surgical team, specialist nursing, microbiology, dieticians, physiotherapy, and psychology. It is important that the wound is reviewed regularly until healing is ensured. Factors such as the local or systemic inflammatory response, wound infection, dehydration, cooling, and nutritional support will influence the outcome.⁶

Immediate Management: Airway, Breathing, and Circulation

Initial management of the burned patient requires an urgent assessment of the airway, breathing, circulation (ABC) of the injured person, an assessment of his or her level of consciousness, and rapid fluid replacement.⁷

All clothing should be removed unless adherent to the burn victim's flesh in which case it should be cooled and soaked with water for formal debridement later. Jewelry, such as rings and wristwatches, should be removed to prevent later complications arising from edema of the extremities. Recent burn injury should be actively cooled with copious amounts of tepid water for up to 20 minutes. Extra caution should be taken in children as their greater surface-area-to-weight ratio may lead to hypothermia. The patient should be nursed in a bed with warm, dry, clean linens to prevent hypothermia. Any blisters should be left intact to minimize the risk of infection, unless they compromise function (e.g., the palm). Antiseptic creams should not be applied initially to intermediate-depth injuries until reassessment has been made.⁶

Inhalation injury should be suspected if there is burn to the face, neck, and/or lips; hoarseness; or evidence of carbon particles (produced by combustion) at the mouth or in the sputum. Inhalation injury is more likely if the victim is found in an enclosed space or if the injury occurred as a result of an explosion.

Smoke inhalation usually consists of carbon monoxide (CO) and/or cyanide poisoning combined with a severe chemical pneumonitis. Modern building construction materials yield significant amounts of cyanide. A carboxyhemoglobin level greater than 10% in a burn victim would be indicative of inhalation smoke injury.

Anoxia is the first complication to consider. Causes are laryngeal obstruction, pulmonary edema, contracted burned skin encircling the chest, carboxyhemoglobin, anemia, and shock. The airway above the glottis is particularly susceptible to obstruction from heat-induced edema.

Inhalation injury may be subtle and often does not appear in the first 24 hours, mandating that patients be observed and have blood gases monitored for at least 24 hours prior to discharge.

Acute inhalation injury requires transfer to a specialist unit for endotracheal intubation and mechanical ventilation. The diagnosis should be made from the history and presenting signs, and intubation prior to transfer may be indicated. This decision should be discussed with the burns unit.

Circumferential Limb Burns

Circumferential burns of the limbs or trunk can cause distal obstruction of the circulation or ventilatory compromise, particularly when they are full thickness, as dermal elasticity is lost. The compressive effect is manifest as interstitial edema increases during fluid resuscitation. It is therefore important to recognize this potential risk in all circumferential injuries, and

Table 27.1 Clinical Features of Epidermal and Partial- and Full-Thickness Burns

Depth	Color	Blisters	Capillary refill	Sensation
Epidermal	Pink or red	No	Present	Sore
Superficial partial thickness	Pink or red	+/-	Present	Painful
Deep partial thickness	Red or pale	+/-	No	+/-
Full thickness	White	No	No	No



Figure 27.6 Escharotomy.

the need for escharotomies should be discussed with the burn unit. Occasionally, escharotomy must be carried out prior to transfer where the journey is prolonged (Figure 27.6). The full-thickness burn is incised down to fat in sterile conditions with diathermy available.

Management on the Burn Unit

Fluid Replacement

A flow sheet outlining the patient's management should be commenced and kept with the patient on arrival on the burn unit. Baseline determination for the major burn patient is shown in Table 27.2. Ideally, the patient should be weighed on admission to the unit, and a full survey of the extent of other injuries should be taken. This will often involve a radiological survey.

The burn represents a large fistula leaking water, electrolytes, and protein. The rate of daily water loss through the breached skin averages 0.30 mL/cm² burned area. If not already sited, large-caliber intravenous lines must be established. Any adult with more than 15% burns (i.e., two whole arms or one whole leg) or a child with more than 10% burns (i.e., one whole upper limb, excluding erythema) will require circulatory volume support. A burn patient will require 2–4 mL of Ringer lactate or colloid solution per kilogram body weight per percent partial- or full-thickness body surface burns in the first 24 hours.

Table 27.2 Baseline Determination for the Major Burn Patient

- Blood: complete blood count, blood type and cross-match, carboxyhemoglobin, serum glucose, electrolytes
- Pregnancy test in women of child-bearing age
- Arterial blood gases
- X-ray: chest x-ray, other x-rays as indicated by injuries
- Time of injury
- Patient's weight
- Estimate of burn injury: extent (% body surface area) and depth of injury
- Comorbidities and medication

In children, plasma equal to the child's plasma volume should be given for every 15% of skin burned. The intravenous fluid rate is adjusted to give one-half of the estimated fluid volume replacement within the first 8 hours after the burn injury and the remainder in the subsequent 16 hours. Fluid requirement calculations for infusion rates are based on time from injury, not from the time fluid resuscitation is initiated. The amount of fluid given should be adjusted according to the individual patient's response to maintain a urinary output of 0.5–1 mL/kg/h (adult) or 1–1.5 mL/kg/h (in children). The goal is to maintain vital organ function while avoiding the complications of inadequate or excessive fluid infusion that can lead to increased tissue edema. No difference in mortality outcomes was seen in a large metaanalysis of patients who received colloid as opposed to crystalloid.⁸

Blood pressure may be difficult to obtain and may be unreliable. Arterial line blood-pressure monitoring is therefore preferable in the intensive care or burn unit setting with cardiac monitoring for signs of dysrhythmia. Electrolyte, acid-base, and fluid balance will need to be meticulously monitored with hourly urine output for which the patient will require urinary catheterization. If there are signs of nausea, vomiting, or abdominal distension, or if the burn involves more than 20% of the total body surface area, nasogastric tube insertion will be required. Blood transfusion is rarely needed.

CO Poisoning

The diagnosis of CO poisoning should be assumed in any injured person found in a smoke-filled environment. Patients with CO levels less than 20% usually have no physical symptoms. Higher CO levels can cause headache, nausea, confusion, coma, and/or death.

CO dissociates very slowly from hemoglobin, but this can be increased by breathing high-flow oxygen via a nonrebreathing mask. Arterial blood gas determinations should be obtained at baseline, but arterial PO₂ does not reliably predict CO poisoning; therefore, 100% oxygen should be administered after baseline carboxyhemoglobin levels have been taken.

Severely burned patients may be agitated or anxious from hypoxemia or hypovolemia rather than from pain. The patient may then respond better to oxygen or increased fluid administration rather than to narcotic analgesics or sedatives that may mask other signs of hypoxemia or hypovolemia. Narcotics, analgesics, and sedatives should be administered in small, frequent doses by the intravenous route only.

Hyperbaric oxygen therapy has been used in the treatment of major burn injury. To be effective, hyperbaric oxygen therapy must be started within 24 hours of the burn (and preferably sooner). It is particularly useful in cases of concomitant smoke inhalation and CO or cyanide poisoning.

Airway Management

Stridor is an indication for immediate endotracheal intubation. Circumferential burn to the neck can lead to swelling of the tissues around the airway and will usually require intubation. If oxygen and humidification are not adequate, positive-pressure ventilation may be needed.

Elevation of the head and chest by 20°–30° reduces neck and chest wall edema. Chest wall escharotomy (burn incised into subcutaneous fat) may be required in the case of a full-thickness burn of the torso, leading to restriction of the chest

wall motion. Local anesthesia is not required, because the skin is rendered insensate.

Nutritional Support

The average sodium loss is 0.03 mmol/cm^2 , and the protein loss is similar to dilute plasma, about 30 g/L . Extensively burned patients will require approximately one-and-a-half times the calories and two to three times the protein needed in health. Feeding may be commenced via the nasogastric tube within 24 hours after the burn injury. If oral feeding is not possible, potassium should be administered by mouth or intravenously to prevent ileus.

Wound Management

Superficial Partial-Thickness Burns

A moist, infection-free environment facilitates the process of reepithelialization. In the case of a superficial partial-thickness injury, an antimicrobial cream plus an occlusive dressing should be applied. Hypafix applied directly to superficial wounds can be useful to preserve mobility and allow washing of the affected part with the dressing intact. It should be soaked in oil (such as olive oil) for an hour before removal and changed at least twice weekly until the wound has healed. Alternatively, tulle gras or a silicone dressing such as Mepitel can be applied, with or without a silver sulfadiazine cream or Acticoat and gauze.⁷

The wound should be cleaned, dressed, and reviewed on alternate days to optimize healing. Antimicrobial cream should be applied using the aseptic method with sterile gloves to avoid nosocomial transmission of potentially pathogenic organisms into the wound. Facial burns heal well and may be left exposed. Any burn that has not healed within 2 weeks should be referred for reassessment.

Deep Partial-Thickness Burns

These injuries are the most difficult to treat and assess. Some deep partial-thickness injuries will heal if the wound environment is optimized to encourage endogenous healing. Other injuries will require excision and grafting.

Delay in reepithelialization beyond 3 weeks is associated with hypertrophic scarring; therefore, all injuries that show no sign of healing by 10 days should be referred to a specialist burn unit for consideration of grafting. Either the depth has been assessed incorrectly or the wound environment has become compromised.

A number of bioengineered skin substitutes have been designed to promote healing. TranCyte is no longer made. Bioengineered skin substitutes, however, tend to be expensive and need to be applied by trained staff in the operating room.

Surgery

With major burns, the goal of therapy is geared toward preservation of life and limb. Wounds that are obviously deep at presentation must be referred early before tissue necrosis triggers multiple organ failure or leads to sepsis. In such cases, more superficial burns may be treated with dressings until healing occurs or fresh donor sites become available.

The best time for surgery is within 5 days of injury to minimize blood loss. The burn eschar is shaved tangentially or excised to deep fascia (Figure 27.7). The aim is to remove the nonviable burnt skin while leaving a bed of viable tissue to allow for grafting or reepithelialization.



Figure 27.7 Shaving a burn. (From Hettiaratchy, S., Papini, R., Dziewulski, P., editors, *ABC of Burns*, BMJ Books, London, 2005. With permission.)

The ideal covering is split-skin autograft from unburnt areas (Figure 27.8). Thickness is usually tailored to the depth of the excision for good cosmesis. Donor sites are often harvested adjacent to the injury to optimize the color match. Unmeshed sheet graft is preferred for the best cosmetic result and is used for the hands and face.

Where donor sites are sparse, or the wound bed is likely to bleed profusely, the graft is perforated with a mesher to allow expansion. Although this improves graft “take” where the wound is bleeding after tangential excision, the mesh pattern is permanent, which some patients may find unsightly.

Rotation of the donor site may be used where unburnt split-skin donor sites are in short supply, or else the excised wound is covered with a temporary cover until donor sites have regenerated for reharvest. Examples of temporary cover include cadaveric allograft from an unrelated donor, xenograft (pigskin is most commonly used), cultured epithelial autograft, or a number of synthetic products.

Cultured epithelial autografts permit greater use of available donor sites. Cultured cells can be applied as sheets



Figure 27.8 Skin graft.

(available after 3 weeks) or in suspension (available within 1 week). The development of synthetic products (such as Integra dermal regeneration template) has enabled surgeons to shave extremely large burns and still achieve physiological closure with potentially lower mortality than was previously possible. These products can be used in combination with mesh graft to improve the final cosmetic result.

Role of Antimicrobials

Unless soiled at the time of injury, an acute burn injury is usually sterile, because the heat from the initial burn is sufficient to kill most skin bacteria. Antibiotics, therefore, should not be routinely commenced following a burn injury but should be reserved for the treatment of secondary infection.

Wounds should be swabbed regularly for bacterial growth and culture sensitivities. The choice of antimicrobials, if indicated, should be based on these results, along with the results of screening swabs, for example, for methicillin-resistant *Staphylococcus aureus* (MRSA).

Tetanus toxoid should be administered. Human antitetanus immunoglobulin should be considered if treatment has been delayed or the wound is heavily contaminated with soil or feces.

COURSE AND PROGNOSIS

A rough calculation of the survival probability for triage purposes can be made using the following formula:

$$100 - (\text{age in years} + \text{area of burn [as a percentage]})$$

For example, a 25-year-old man with a 30% burn can expect a 45% ($100 - [25 + 30]$) survival; however, advances in burn management have made such formulae all but obsolete. A more accurate method, taking into account the age of the victim and whether the victim had any inhalation injury, has been described.⁹ Such calculations are useful in informing clinical decision making and providing the carers and family with more realistic expectations.

CRITERIA FOR REFERRAL TO A BURN UNIT

Although not all the patients in the categories in Table 27.3 will require transfer to a specialized burn unit, consultation with the appropriate center should take place at presentation to plan further management and anticipate possible complications. Any complex injury should be referred.

Table 27.3 Criteria for Referral to a Burn Center

- Deep burns involving
 - 10% or more of the total body surface area in adults
 - 5% or more of the total body surface area in children
- Burns to the face, eyes, ears, hands, feet, genitalia, perineum, inner joint surfaces
- Inhalation injury
- Significant chemical and electrical burns, including lightning injury
- Burn injury with any of the following:
 - Major preexisting illness such as diabetes that could complicate management and recovery
 - Suspected child abuse and neglect
 - Concomitant injury

Full-thickness injuries have no regenerative elements left. Unless they are very small, they will take weeks to heal and undergo severe contraction. They should be referred for surgery as early as possible.

COMPLICATIONS

The number and complexity of complications will depend on the premorbid state of the patient as well as the extent and type(s) of injury.

Compartment Syndrome

Raised intracompartmental pressure due to progressive tissue damage and inflammation can impede compartmental blood flow leading to ischemia and anoxic necrosis. Fasciotomy and nerve decompression (requiring clinical vigilance and close liaison with the surgical team) should be undertaken prior to the onset of irreversible damage.

Infection

Unless there is debris in the wound, the thermal energy from the burn will kill the commensal flora of the skin. The routine use of broad-spectrum antibiotics on admission is not recommended, unless the wound involves areas with a high bacterial load, such as the perineum or feet, or where the wound has been soiled.

Exposed devitalized flesh provides a warm, moist culture medium, and a sterile wound can quickly become colonized from adjacent unburned areas, when the skin has lost its integument. Even so, it will normally take approximately 5 days for an infection or significant colonization to become established in a previously sterile site.

If a wound infection is suspected or the patient develops any signs of sepsis (raised temperature, raised C-reactive protein, raised white cell or neutrophil count), then wound swabs and blood cultures should be taken before embarking on “blind” antimicrobial therapy. The choice of antimicrobials will depend on the unit guidelines based on the local endemic resistance pattern and cost. Close liaison with the microbiologist is essential to avoid inappropriate prescribing.

The emergence of multiresistant organisms (including resistant *Pseudomonas* spp., *Acinetobacter baumannii*, MRSA, and vancomycin-resistant *Enterococcus*) within burn units has become an increasing problem. The overall attributable mortality rate for these organisms is high, and once established, eradication from the burn unit can be difficult due to their ubiquitous nature and ability to survive for prolonged periods on inanimate surfaces.

Thromboembolic Disease

Burn injury, coupled with fluid loss and a prolonged period of rest in a warm environment, will increase plasma fluid viscosity. Prophylaxis with a low-molecular-weight heparin is recommended but can be delayed until after initial debridement and shave excision procedures. The clinical team should be mindful of late thromboembolic complications such as deep vein thrombosis or pulmonary embolus. The D-dimers will be of limited use in the context of a recuperating burn patient, and diagnosis will rely on Doppler ultrasound or venogram. Treatment will be as for a general surgical patient with a target international normalized ratio of 2.5, range 2–3.

OTHER TYPES OF BURN INJURY

Chemical Burns

Chemical burns may result from exposure to acids, alkalis, and petroleum products. Alkali burns tend to be deeper and more serious than acid burns.

Management involves washing the burn with copious amounts of running water for at least 20–30 minutes (longer for alkali burns). Certain chemicals will produce toxic products with only a small amount of water, so it is important to use a copious amount of water to dilute the effects of the chemical. If the toxic chemical is in powder form, then the powder should be brushed away before irrigation with water.

Ocular chemical injury requires continuous irrigation for at least 8 hours in the case of alkali burns.

Electrical Burns

Electrical burns account for approximately 3% of burn patients attending specialized centers (Figure 27.9). These burns are arbitrarily classified as high- or low-tension injuries depending on the voltage, with high-tension burns resulting from shocks of greater than 1000 volts. Most electrical burns, however, are the result of low-tension domestic appliances. Other sources of current are overhead high-voltage power lines and rail electrification, including the “third rail.” These overhead power lines pose a threat not only to workers but also to sports enthusiasts involved in pursuits such as fly-fishing, kite-flying, hang-gliding, and parachuting.^{10,11}

Removal of bodies from overhead cables will require electrical isolation at the point of recovery.

Electrocution causes reflex muscle contraction. Firefighters are thus trained to feel their way out of a smoke-filled room using the back of the hand rather than the palm so that if an exposed live wire is encountered the shock will produce a repulsion of the limb rather than a grasp reflex.

The severity of electrical burn injury is related to the voltage, duration of contact, and thickness and wetness of the skin.



Figure 27.9 Electrical burn.

Electrical burns are often more serious than they appear on the surface. Any organ between the entry and exit point can be injured. High-voltage contact results in significant rhabdomyolysis with myoglobinuria and subsequent risk of renal failure. Death may occur as a result of cardiac stunning.

The histology of a skin injury shows a distinctive vertical elongation of the nuclei of the cells of the basal layer. The superficial epidermal cells may show similar changes. Dermal-epidermal separation may be present with elongated degenerated cytoplasmic processes from the basal cells protruding into this space.

Lightning Strike

Approximately 100 deaths occur every year from a lightning strike in the United States. Millions of volts are conducted through a channel of approximately 1 cm diameter in less than a few milliseconds. Although 90% of victims survive the lightning strike, up to 70% will suffer late organic or psychological effects.

The classic dermatologic injury is an arborescent or feather-like lesion known as a Lichtenberg flower. Small burns at the site of metal objects held in the hands or pockets may also be evident.¹²

Therapy is directed toward management of the extracutaneous complications that include respiratory arrest, gastric dilatation, ileus, cerebral edema, rupture of the tympanic membrane, and fractures.

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Emergency dermatoses of the anorectal regions

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Anorectal disorders are commonly encountered in the practice of emergency medicine. Almost all anorectal disorders once diagnosed and treated in the emergency department need appropriate follow-up for further possible diagnostic procedures and definitive treatment. Dermatologic disorders localized in the anorectal region seriously affect the quality of life for patients of all ages. A spectrum of anorectal disorders ranges from the benign with mild symptoms to potentially life-threatening and urgent situations. Many disorders can affect the perianal area, and the most common ones include hemorrhoids, pruritus ani, anal fissures and fistulas, rectal prolapse, anal carcinoma, fecal incontinence, pelvic floor dyssynergia, and proctalgia fugax.¹

Symptoms related to anorectal disorders are nonspecific, and the main complaints for the patients are pruritus and pain. The most common exogenous causes exaggerating anal pruritus are the use of harsh soaps, perfumes or deodorizers, excessive wiping with toilet paper, and synthetic underwear or tight, warm clothing, which promotes sweating. Other causes include dermatophytoses, parasitic infections, psoriasis, and neoplastic disorders, including Paget disease and Bowen disease. Psychologic factors may also contribute.

On physical examination, excoriations can often be seen, and in advanced cases, secondary bacterial infections with edema, erythema, ulceration, and an exudate are present. Treatment should be aimed at the causative agent, and the most effective local therapy includes topical corticosteroid and anesthetics.²

ANORECTAL DISORDERS

One of the most prevalent anorectal disorders is hemorrhoids. These represent conglomerates of varicose veins, supporting tissues, and overlying mucous membrane or anorectal skin. An internal hemorrhoid is the part of the varicosity above the dentate line, and an external hemorrhoid is the distal part, which is covered with anorectal skin. Prolapsed internal hemorrhoids extend into the anal canal or through the anus. A thrombosed external hemorrhoid arises from a ruptured blood vessel. The bleeding is usually minimal, appearing as bright red on the stool or toilet paper. Pain occurs only with prolapsed internal hemorrhoids and thrombosed external hemorrhoids. External hemorrhoids can be diagnosed by inspection, but the diagnosis of internal hemorrhoids requires anoscopy. In some cases, strangulated hemorrhoids can be presented as an emergency situation. For mild hemorrhoids, treatment consists of a soft diet and stool softeners. Sitz baths and suppositories or ointments, containing benzocaine or other local anesthetics, can relieve symptoms. Band ligation, sclerotherapy, hemorrhoidectomy, cryosurgery, and laser therapy are other treatment alternatives.^{2,3}

Anal fissures are longitudinal breaks in the squamous epithelium of the anal canal. They may be superficial or deep, and an external skin tag often forms at the lower end of a chronic fissure. Risk factors for anal fissures might include hard bowel movements, rough fecal debris, straining at stool, diarrhea, or trauma to the anal canal. The main symptom is severe pain, which is aggravated by defecation with accompanying minor bleeding. Fissures usually occur at the posterior midline of the anus and are visible when the patient strains.²

Anal fistula is a sinus tract between the rectum and the skin. They commonly result from a perianal or ischiorectal abscess caused by inflammation of rectal crypts or glands. Inflammatory diseases such as Crohn disease, tuberculosis, lymphogranuloma, and diverticulitis may also cause fistula formation. The main symptom is perirectal pain with pus or blood seen on toilet paper. Most anal fistulas open near the anus. During initial examination, probing the entire tract may be possible but locating the internal opening is usually difficult prior to surgery. As the first-line treatment of fistulas is surgical repair, in some patients it can be the subject of an emergency approach.³

Rectal prolapse is protrusion of a part of the rectum through the anus. Mucosal prolapse involves only the mucosal layer of the rectum, whereas complete prolapse involves all layers. The underlying defect is a long, lax sigmoidorectal mesentery that cannot keep the rectum in position. The main sign is protrusion of the mucous membrane or the rectum, often palpated as an anal mass by the patient. It can cause pain and discharge of mucus and blood from the inflamed mucosa. During physical examination, the degree of prolapse can be determined by inspection and palpation. Conservative therapy such as avoidance of straining, lifting, and excessive standing provides temporary relief; however, surgical repair is necessary in most patients.^{3,4}

With a general overview of these dermatoses, bacterial infections comprise the most serious and life-threatening conditions of the anorectal region. Making early and prompt diagnosis is crucial, because a delay of the treatment may cause a marked increase in both morbidity and mortality. Emergency dermatoses involving the anorectal area are listed in Table 28.1.

STAPHYLOCOCCAL CELLULITIS

The anorectal area provides a humid environment with high temperature and is exposed to constant pressure as well as friction. *Staphylococcus aureus* can be colonized both in the inguinal and perianal region. Severe involvement with furunculosis and abscesses suggests an overlap with hidradenitis suppurativa. Cellulitis and abscess formation can aggravate cysts, sinuses, and fistulas.⁵

Table 28.1 Emergency Dermatoses in the Anorectal Region

Staphylococcal cellulitis
Streptococcal dermatitis/perianal cellulitis
Perianal abscess
Ecthyma gangrenosum
Necrotizing infections

Cellulitis, caused by staphylococcal species, presents with erythema, heat, swelling, and pain or tenderness. The border of the lesion is diffuse and not well demarcated, unlike erysipelas. Severe cellulitis may also show hemorrhagic bullae and can progress to dermal necrosis, fasciitis, or myositis. Anorectal infections in the case of malignancies can be serious and potentially life threatening. Perianal infiltration, ulceration, or abscess formation occurs in case of hematologic malignancies and may rarely be the presenting feature.⁶

Some cases of anorectal cellulitis may respond to antimicrobials alone, but necrotizing fasciitis and Fournier gangrene carry a high risk and show poor response to therapy.⁶

Without effective treatment, complications are common—fasciitis, myositis, subcutaneous abscesses, and septicemia. It is difficult to determine the timing of surgery, especially for abscess formation.⁷

STREPTOCOCCAL DERMATITIS/ PERIANAL CELLULITIS

Group A beta-hemolytic *streptococci* and very rarely *Staphylococcus aureus* are the main causes of infectious dermatitis. It is mostly seen in children below the age of 8 years. Streptococcal dermatitis, as well as other streptococcal infections like tonsillitis or pharyngitis, is associated with the increased risk of acute guttate psoriasis. Streptococcal infections may also complicate with nephritis.⁸

Streptococcal dermatitis often presents with perianal erythema, edema, and soreness suggesting ongoing inflammation. Satellite pustules can be helpful in differentiating from intertrigo. Painful defecation and pruritus are often the leading symptoms. On dermatologic examination of the perianal region, there is a sharply demarcated erythema.^{8,9}

Recurrent streptococcal perianal cellulitis is attributed to lymphatic damage, which, although sometimes clinically unapparent, predisposes to further infection and lymphatic impairment manifesting as lymphedema. Venous insufficiency often predisposes to recurrent attacks of streptococcal cellulitis.⁹

Systemic penicillin or topical mupirocin in cases of milder conditions are the initial treatment approaches. Depending on the resistance patterns and severity of the disease, erythromycin can also be prescribed.⁶ Both streptococcal and staphylococcal infections may be fatal, especially in infants and debilitated or immunosuppressed patients.^{8,9}

PERIANAL ABSCESS

Perianal and anorectal abscesses are usually characterized by painful swelling and suppuration, often accompanied by an anal fistula. A perianal abscess occurs due to microbial infection and inflammation of the anal glands. Predisposing factors for the development of perianal abscesses include chronic illnesses, such as diabetes mellitus, Crohn disease, hidradenitis suppurativa, malignancies like colon or more commonly rectal carcinoma, poor hygiene, immunodeficiency syndromes

or acquired causes of immunity failure like HIV infection, transplantation, or chemotherapy.¹⁰

ECTHYMA GANGRENOSUM

Ecthyma gangrenosum is an infectious dermatitis caused by *Pseudomonas aeruginosa*. It is most commonly observed in patients with immunosuppression such as with leukemia, severe burns, pancytopenia or neutropenia, functional neutrophilic defect, terminal stage malignancies, or some severe chronic illnesses. Ecthyma gangrenosum usually occurs in the presence of *Pseudomonas aeruginosa* bacteremia.¹¹

Healthy infants may also develop ecthyma lesions over the perianal area after antibiotic therapy during the first year of life. Due to intractable diarrhea and alteration of the normal bowel flora, severe diaper dermatitis and maceration of the area facilitate the development of ecthyma gangrenosum.^{12,13}

Moist areas such as the axilla, perineum, and buttocks are more prone to *Pseudomonas* infections. Swimming pools, Jacuzzis, and other high humidity environments are main sources of *Pseudomonas* species. Clinically a narrow, pink to violaceous halo surrounds tender vesicles, pustules, and bullae. With time, the lesions become hemorrhagic and rupture to form round ulcers with necrotic black centers. The infection mainly affects buttocks and extremities, but in rare cases the anorectal area can also be involved. The diagnosis is mainly clinical, and necrotic vesicles and pustules are the main distinguishing lesions. Ecthyma gangrenosum diagnosis can be confirmed by observing gram-negative bacilli on Gram stain and *Pseudomonas aeruginosa* growth in the bacterial cultures from the samples obtained by vesicle content. Blood cultures may also be helpful in case of systemic toxicity symptoms.^{14,15}

Treatment of ecthyma gangrenosum should be started promptly. Especially local infections in infants or patients with debilitating illnesses should be regarded as potentially dangerous, for systemic extension occurs readily.^{14,15} Treatment includes administration of intravenous anti-*Pseudomonas* antibiotics. Ceftazidime, gentamicin, piperacillin, azlocillin, tobramycin, and amikacin may be used in appropriate combinations. In every case where antibiotics are contemplated, it is important to base the therapy on the results of in vitro sensitivity tests.¹⁶ Acetic acid compresses, potassium permanganate soaks, povidone or silver sulfadiazine cream may be useful, but topical antibiotics are generally disappointing. In case of extensive lesions, debridement followed by topical and systemic antibiotherapy is the treatment of choice.¹⁶

If there is a delay in diagnosis or the initiation of the therapy, the risk of systemic involvement increases. Immunosuppression can also complicate the infection and increase morbidity as well as mortality.¹⁷

NECROTIZING INFECTIONS (GANGRENOUS CELLULITIS, INFECTIOUS GANGRENE, CREPITANT SOFT-TISSUE WOUNDS)

These groups of infections are localized within soft tissues of the deep aspect of the dermis, adipose tissue, and subcutaneous fascia, where the hallmark of infection is extensive necrosis accompanying cellulitis. The affected patient is usually severely ill and toxic, and there is a mortality rate of over 45% in some series.¹⁸ The extent of infection is variable among different cases, in some it is restricted to a zone bound by fascia, and in others, infection extends to involve muscle and deep vessels.

Table 28.2 Classification of Necrotizing Infections

1. Necrotizing fasciitis
 - Streptococcal gangrene (type 2 necrotizing fasciitis)
 - Type 1 necrotizing fasciitis
 - Synergistic necrotizing cellulitis
 - Fournier gangrene
2. Clostridial soft-tissue infections
 - Anaerobic cellulitis
 - Anaerobic myonecrosis
 - Spontaneous, nontraumatic anaerobic myonecrosis
3. Meleney progressive bacterial synergistic gangrene
4. Gangrenous cellulitis in the immunosuppressed patient
5. Localized areas of skin necrosis complicating conventional cellulitis

Common predisposing factors include trauma, infection, diabetes mellitus, and previous surgery.¹⁸

These infections are characterized by rapid and uncontrollable progression and thus increased mortality. Initially, necrosis appears with cellulitis, which is often accompanied by considerable toxemia. At the onset, patients may complain of vague mild pain, tenderness, and minor erythema. After the rapid evolution of the infection, vesicles, pustules, and bulla formation, together with frank necrosis, can be observed. The infection can invade both superficial and deep fascia with secondary changes in the overlying soft tissues.⁵

These clinical syndromes are caused by the infection of wounds with various species of *Clostridium* (*C. perfringens*, *C. oedematiens*, *C. septicum*, *C. histolyticum*) in combination with group A beta-hemolytic streptococci, anaerobic streptococci, and often with aerobic organisms such as *Proteus*. The incubation period varies from 12 hours to 5 or 6 days, according to the species predominantly involved.¹⁹

Dermatological examination revealing edema and crepitation demonstrating the presence of gas can be felt over the affected area. Deep and dirty wounds in the muscular regions of the body are most susceptible. The affected area becomes painful and swollen, and there is an increased amount of serous discharge from the wound. Severe toxemia, tachycardia, and prostration may rapidly develop.²⁰

There are various numbers of overlapping severe gangrenous and necrotizing diseases that may affect the anorectal and perineal region. All of these infections are life-threatening and can be fatal unless treated immediately with the proper approach.^{21,22} In Table 28.2, necrotizing infections are classified.

NECROTIZING FASCIITIS

Necrotizing fasciitis is a life-threatening infection, characterized by the necrosis of subcutaneous tissue and fascia. There are two types of necrotizing fasciitis infection: type 1 and type 2.²³

Type 1 necrotizing fasciitis most commonly occurs on an extremity (Figure 28.1), abdominal wall, and rarely, the perineum. The port of entry is thought to be an incision or even a surgical wound. This infection is caused by a mixture of facultative and anaerobic microorganisms, most of which are present in the subcutaneous tissues following surgery, bowel perforation secondary to neoplasm or diverticulitis, trauma, or parenteral drug abuse. Diabetes mellitus and malnutrition are two major predisposing factors for necrotizing fasciitis. The infection may follow entry of group A streptococci,



Figure 28.1 Type 1 necrotizing fasciitis localized on the body and extremity; under treatment.

Staphylococcus aureus, *Aeromonas hydrophila*, *Vibrio vulnificus*, or a mixture of other bacteria, including at least one anaerobic organism into the skin.^{24,25}

From the clinical point of view, it is often difficult to distinguish type 1 necrotizing fasciitis from streptococcal gangrene. Type 1 necrotizing fasciitis seems to begin more slowly than type 2. At the beginning, there is mild tenderness in the involved area, followed by marked edema, erythema, warmth, and pain. The onset may be indolent, causing a false sense of lack of urgency, and swabs from the skin surface at this stage are usually negative. Within several days, the skin becomes purple, multiple bullae develop, and frank cutaneous gangrene is seen. The edema around the wound continues to spread and is associated with first bullae and then black slough formation. Superficial nerves of the subcutaneous tissue may be damaged due to infection, and thus the pain gradually diminishes.²⁶ Crepitation is often present, especially in patients with diabetes mellitus or if there are gas-forming anaerobes. Type 1 necrotizing fasciitis is usually accompanied by tachycardia, irritability, and hypotension.²⁷

Type 2 necrotizing fasciitis is more common in body parts other than the anorectal region. In 20% of the patients, group A beta hemolytic *streptococci* are the responsible microorganisms isolated from the lesions²⁸; however, in almost all cases of perineal infections, there is a mixture of different microorganisms complicating the infection. The major mechanisms of tissue destruction include deformation of erythrocytes and endothelial cell damage leading to thrombus formation, hemorrhage, and tissue necrosis. The combination of kinin activation, coagulation, and fibrinolysis leads to a disseminated intravascular coagulation-like state. Many streptococcal enzymes, such as hyaluronidase, streptolysins, and streptokinases, also play a major role. The infection usually develops after minor trauma or surgery. The necrotizing area expands rapidly and becomes dusky with bulla and a necrotic crust. Crepitation may be present, especially in mixed infections. There is almost always a high-degree fever and a general malaise, with possible changes in the mental status of the patient. As the disease progresses, the neurons are destroyed, and thus the pain decreases eventually.²⁹

Histopathologic examination of necrotizing fasciitis reveals a massive destruction of the soft tissue and fascia with thromboses and liquefaction. The muscle tissue may be secondarily damaged.²⁸

The diagnosis must be made promptly on clinical basis, supported by the bacterial examination of the specimens from the lesion. Blood cultures should be taken prior to antimicrobial therapy. Proper anaerobic techniques should be employed to obtain organisms in case of suspicion of clostridial species. Radiology may confirm gas in the tissues.³⁰

The most important and urgent therapeutic approach is extensive surgical debridement of all damaged tissue, both the infected area and the immediate surrounding region. Complete removal of necrotic tissue is required. The overlying skin is usually surgically removed, although in some cases this can be laid back as a flap once the necrotic tissue has been removed. Local debridement or incision and drainage are usually not effective and result in recurrence of the existing infection. For systemic therapy, penicillin G, 30 million units daily for at least 10–14 days, in combination with clindamycin 600 mg three times daily for 1–2 days for anaerobic infections is necessary.³¹ Other alternatives are metronidazole and imipenem, but one must keep in mind that antimicrobial therapy is only an adjunct to surgery, and if antibiotics are given without surgical intervention, therapy is rarely successful. Intravenous immunoglobulins and organ-specific supportive measures are also recommended. Heparinization should be used to prevent disseminated intravascular coagulation. The role of hyperbaric oxygen in decreasing mortality rates remains controversial due to the lack of controlled studies and may lead to delays in essential surgery.^{32,33}

Fournier Gangrene

Fournier gangrene is a variant of necrotizing fasciitis, localized to the genital area and perineum. The exact incidence of the infection is uncertain, although it seems to be higher in Asia and Africa. Necrotizing gangrene of the genitalia and perineum is a progressive and potentially life-threatening infection. This is considered a surgical emergency with a mortality rate of 40%.³⁴

In 1833, Jean-Alfred Fournier (1832–1914) first described fulminant gangrene of the penis and scrotum in five men. Initially, Fournier gangrene was defined as an idiopathic entity, but today perineal or genital skin infections are shown to be responsible for the vast majority of cases. Anorectal or urogenital and perineal trauma, including pelvic and perineal injury or pelvic interventions, are other causes of Fournier gangrene.³⁵ The most common foci include the gastrointestinal tract (30%–50%), followed by the genitourinary tract (20%–40%), and cutaneous injuries (20%).^{35,36}

The organisms isolated include gram-negative bacilli, gram-positive cocci, and anaerobes.³⁷ Cultures from the wounds commonly show polymicrobial infections by aerobes and anaerobes, which include coliforms, klebsiella, streptococci, staphylococci, clostridia, bacteroids, and corynebacteria. On average, at least three organisms are cultured from each diagnosed patient.³⁸ Most of these are normal commensals in the perineum and genitalia, which, because of the impaired host cellular immunity, become virulent and act synergistically to invade tissue and cause extensive damage.³⁹ Even though *Escherichia coli* has been reported to be the most common organism isolated from the wound, it could be because

of the commensal nature of these organisms in the perineal region. Anaerobes are less frequently isolated than expected, which could be due to technical faults.³⁸ Aerobes and anaerobes synergistically lead to the production of many exotoxins and enzymes like collagenase, heparinase, hyaluronidase, streptokinase, and streptodornase. The platelet aggregation and complement fixation induced by the aerobes and the heparinase and collagenase produced by the anaerobes lead to microvascular thrombosis and dermal necrosis, which cause tissue destruction and the spread of infection.^{40,41}

Fournier gangrene is more frequently observed in men and is most commonly seen between the ages of 38 and 44. It is rare in children; however, cases after neonatal circumcision have been observed. In men, the infection typically affects the scrotum, occasionally invades the penile area, and less frequently, involves the perineum and abdomen. The muscle layer and testes are usually spared. In women, the infection tends to involve both the vulva and the perineum.⁴²

Fournier gangrene has been shown to have a predilection for patients with diabetes, as well as with long-term alcohol misuse, malignancies, vascular disease, neutropenia, human immunodeficiency virus-positive patients, and transplant recipients; however, it can also affect patients who have nonobvious immune compromise.⁴³

Diabetes mellitus is reported to be present in 20%–70% of patients with Fournier gangrene, and chronic alcoholism in 25%–50% of patients.^{44,45}

The emergence of HIV into epidemic proportions has opened up a huge population at risk for developing Fournier gangrene. The impaired defense mechanisms in the host help the infection proceed unchecked, and at alarming speed, along the fascial planes.⁴⁶

Fournier gangrene can show different clinical presentations, from insidious onset and slow progression to rapid onset and fulminant course. Early recognition and aggressive treatment are important. The infection commonly starts as a cellulitis adjacent to the portal of entry, commonly in the perineum or perianal region. A discrete area of edema and erythema on the scrotum progresses to advanced skin necrosis rapidly in a few days. Local signs and symptoms are usually dramatic with significant pain, swelling, and crepitation in the scrotum, perineum, or suprapubic region due to the presence of gas-forming organisms.⁴⁷ Foul-smelling drainage may indicate anaerobic infection. Purplish discoloration of the scrotum and perineum is recognized as the “red flag” sign, and it rapidly progresses to frank gangrene. As the subcutaneous inflammation worsens, necrotic patches start appearing over the inflamed skin and progress to extensive necrosis. Unless aggressively treated, the patient can rapidly progress to sepsis with multiple organ failure, the common cause of death in these patients.^{48,49}

At the initial phase, the infection is superficial and limited to subcutaneous tissue, but with time it extends to the base of scrotum, penis, perineum, and abdominal wall along fascial planes (Figure 28.2).⁵⁰ The spread of infection is along the fascial planes and is usually limited by the attachment of the Colles fascia in the perineum.

The testes are usually spared as their blood supply originates intraabdominally. Involvement of the testis suggests retroperitoneal origin or spread of infection.⁵¹ Fournier gangrene is histologically characterized by obliterative endarteritis and thrombosis of the subcutaneous vessels, fascial necrosis,



Figure 28.2 Fournier gangrene. (Courtesy of Lawrence Charles Parish, MD, Philadelphia, PA.)

and leukocyte infiltration. Ultrasound, x-ray, or magnetic resonance imaging may reveal gas or testicular involvement and may be a clue to clostridial infection.⁵²

Early recognition and aggressive treatment are important. Management options include resuscitative measures, broad-spectrum antibiotics, and surgical debridement.⁵⁰ The evidence for use of hyperbaric oxygen remains controversial.⁵³ Despite optimal appropriate treatment, the disease has high mortality rates, between 25% and 75% but lower mortality rates have also been reported possibly by means of proper supportive measures.^{44,54}

SYNERGISTIC NECROTIZING CELLULITIS (NECROTIZING CUTANEOUS MYOSITIS, SYNERGISTIC NONCLOSTRIDIAL ANAEROBIC MYONECROSIS)

This variant of necrotizing fasciitis has a high mortality rate with the involvement of all soft tissue structures including muscle. It is a painful, progressive, and polymicrobial infection that can cause high rates of mortality. Elderly patients with chronic illnesses, such as diabetes mellitus, renal or cardiac failure, obesity, or multiorgan defects, have increased risk for synergistic necrotizing cellulitis.^{55,56}

Perineum is the most commonly involved area but rarely the anterior abdominal wall, inguinal area, and thigh region can also be affected. During the early stages of the disease, there is mild pain, and the patients are usually afebrile or have only a low-grade fever, without systemic toxicity. The initial skin lesion is a small area of a necrotic crust or a reddish-brown blister with extreme local tenderness. After the formation of an ulcer, there is almost always a foul-smelling drainage and rapid expansion of the lesion follows.⁵⁷

Examination of the purulent material reveals both gram-positive and gram-negative organisms with very few or no neutrophils. Facultative and anaerobic bacteria are frequently isolated from the lesions. Through the distorted areas of the skin barrier, extensive gangrene of the superficial tissues and fat

can easily be visualized. In approximately 25% of the patients, crepitation is due to gas formation.⁵⁸

Perirectal and ischiorectal abscesses are two major predisposing factors leading to synergistic necrotizing cellulitis. Treatment is similar to streptococcal necrotizing fasciitis, including wide and deep debridement of the area. According to the culture results, proper antibiotherapy should also be initiated.⁵⁹

PROGRESSIVE BACTERIAL SYNERGISTIC GANGRENE (MELENEY GANGRENE)

Frank Meleney (1889–1963) first described synergistic gangrene in the 1930s, based on studies done in vivo with rabbits. According to the microbiologic studies, this infection is usually associated with a microaerophilic *Streptococcus* or anaerobic *Streptococcus* at the advancing margin and *S. aureus* in the central ulcerated area, together with *Bacteroides* spp. or other anaerobes, as well as gram-negative bacteria.⁶⁰

The location of the infection is usually drainage sites after an abdominal operation, on an incision of the chest wall following abdominal or thoracic infection, the exit site of a fistulous tract, or in a chronic ulcer. It can rarely be seen in the perineum. Also, progressive synergistic gangrene may occur without apparent injury to the skin surface.⁶⁰

At the initial stages of the infection, there are usually a local erythema, tenderness, and swelling, which eventually progress into a painful and superficially enlarging shaggy ulcer. The lesion typically has three zones: a central area of necrosis; a surrounding zone of violaceous, tender, erythematous tissue with necrotic margins; and an outer zone of bright red erythema and edema. The lesion progressively enlarges without treatment and may involve most of the abdominal or perineal area (Figure 28.3). Rapid deterioration of the patient's clinical state occurs with dehiscence of the surgical wound and toxemia.⁶¹

It is usually difficult to diagnose bacteriologically. Careful culturing with appropriate swabs being taken for anaerobes



Figure 28.3 Synergistic gangrene, following drainage of perianal abscess.

should be carried out; however, waiting for the results should not delay the initiation of the therapy. The presence of gas in the tissue may suggest the diagnosis, but its absence does not exclude the infection. Computed tomography is a more precise method than x-ray for demonstrating gas in tissues.⁶¹

Prompt treatment is necessary with surgical exploration of the wound, excision of the ulcer, together with necrotic margins and appropriate antimicrobials according to the Gram stain and culture results. Penicillin in high dosage, in combination with other agents, depending on the sensitivity of organisms isolated, is necessary, but the most important aspect of the therapy is surgical intervention.⁶¹

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Emergency management of sexually transmitted diseases and other genitourethral disorders

Michael Waugh

This chapter is based on practical clinical experience of the author in the management of sexually transmitted diseases since 1969 in the United Kingdom. In the United Kingdom, genitourinary medicine (sexually transmitted infections [STIs] covers human immunodeficiency virus/acquired immune deficiency syndrome [HIV/AIDS], as well as sexually transmitted diseases [STDs]). It is a separate specialty and requires considerable postgraduate study in all aspects of sexual health. Although emergencies in the acute internal or medical sense are rare, rapid and astute clinical management of many of the conditions encountered is necessary.

Patients are usually concerned when they think that they might have contracted an STD. Accurate diagnosis is needed so that necessary medication (whether it be antimicrobial, antifungal, or antiviral) may be given. Fast diagnosis is needed to abort infection, wherever possible, and to prevent immediate and long-term consequences to the patient. When an STI has been contracted, it is imperative that an easily understood explanation and education also be given to the patient with the reasons given why contact tracing (partner notification) must be pursued for sexual contacts. Follow-up is necessary not only to make sure that any immediate infection or infections are cured, but also to make sure that adequate care is taken to test for infections such as syphilis and HIV, which may well require testing not only on immediate presentation but also 1 month and 3 months after initial presentation. It is essential under any public health and legal system to maintain confidentiality of the patient and to explain, if necessary, to the patient what that means.

Many patients will nowadays use resources on the Internet to gain information. This method is frequent, and the good physician will work with that system and help the patient to enhance his or her knowledge rather than decrying Internet information. In the United Kingdom, the Department of Health has recognized the importance of early access to STD services and has set a goal that any patient should be offered an appointment within 48 hours of contracting the service, which must have well-publicized easy accessibility.¹

NON-STD CONDITIONS

Conditions that are not STDs but that may present to venereologists and must never be missed include the following items.

Torsion of the Testicle

Torsion of the testis is not a common condition. The author has only seen one case presenting in almost 50 years in practice. It occurs with equal frequency in incompletely and fully

descended testes. Taking into consideration that incomplete descent is present in less than 1% of men, it is obvious that torsion of an incompletely descended testis occurs relatively more frequently than that of a completely descended testis. The highest incidence is in men between 15 and 25 years old, and the second most common incidence is in infants.

The symptoms vary with the degree of torsion present. Most commonly, the patient experiences sudden and agonizing pain in the groin and lower part of the abdomen and vomits. In about one-quarter of patients, the first symptom is a dull ache in the loin or hypogastrium. It is insufficiently appreciated that true testicular pain is situated in the lower aspect of the abdomen at the level of the internal inguinal ring. It might be considered that the diagnosis is simple. It can be impossible to distinguish torsion of an imperfectly descended testicle from a strangulated inguinal hernia until the parts have been displayed by operation. Torsion of a completely descended testicle is a less difficult problem; sometimes, the actual twists in the cord can be felt, thus establishing the diagnosis.

Torsion of the testicle may stimulate an acute epididymo-orchitis; after approximately 6 hours, the skin of the scrotum becomes reddened, and the temperature may be raised 37.2°C. Elevation of the scrotum usually relieves the pain in epididymitis but increases it in torsion.² Scrotal ultrasound is not a satisfactory way to make a diagnosis of torsion of the testicle, and if mumps and an acute infectious epididymo-orchitis are excluded, surgical exploration should not be delayed by diagnostic imaging.³

Ectopic Pregnancy

Various degrees of pelvic inflammatory disease (PID), caused mainly by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, but also by *Mycoplasma hominis* and anaerobes, are frequently seen, but a condition in which there should be a high index of suspicion is ectopic pregnancy.⁴

By definition, ectopic pregnancy refers to any nonintrauterine pregnancy. Although ectopic pregnancies may be ovarian, cervical, or intraabdominal, the vast majority are tubal, having an incidence of 1:200–400 pregnancies. There may be a history of a previous ectopic pregnancy, previous surgery, pelvic infection, endometriosis, or in vitro fertilization, but approximately half occur with no predisposing cause.

Clinical Features

Clinical features range from no symptoms at all; to right, left, or bilateral lower abdominal pain; bleeding per vagina; intraabdominal hemorrhage (peritonism and shoulder tip pain); and collapse. Pelvic examination should be gentle to avoid tubal

rupture. An ultrasound investigation is often useful. It should be noted that a gestational sac may be confused with a pseudosac (due to fluid in the thickened endometrium), which is seen in 20% of ectopic pregnancies and which lacks the echogenic ring of a gestational sac. A true sac is usually smooth with a double rim, is eccentrically placed, and may contain a yolk sac.

Management

Immediate referral for acute emergency gynecological assessment is essential. The management of shock and the setting up of two intravenous (IV) lines is urgent as is the setting up and patient cross-matching for 6 units of red cell concentrate.

Paraphimosis

Although this condition has none of the serious consequences of the previous two conditions, it is not infrequently seen turning up in young men attending STD clinics, especially in countries where men are uncircumcised. The tight prepuce has been retracted but cannot be returned, and it is constricting the glans, which is engorged and edematous. The patient is usually frightened. The diagnosis is apparent at a glance.

The surgical textbooks recommend injection of normal saline containing 150 turbidity units of hyaluronidase injected into each lateral aspect of the swollen ring of the prepuce. Usually, within 15 minutes the swelling is much reduced; this is, however, not always available. Soaking the swollen parts in ice water for the same amount of time and giving the patient 5 mg of diazepam while lying down usually allows the doctor to reduce the paraphimosis by bilateral gentle pressure of the thumbs on the glans while holding firmly but not painfully the prepuce proximal to the paraphimosis. The paraphimosis disappears. If that is impossible, or if the paraphimosis has been there too long or the patient will not relax, a urologist needs to be consulted for reduction under anesthesia and later circumcision.

Squamous Cell Carcinoma of the Penis

Although rare, this is a condition that must not be missed; it is a serious cancer with a high mortality. In STD clinics for men, one or two cases will turn up annually, usually in older men, often having noticed something wrong for some length of time but for one reason or another not having sought help from a doctor. Risk factors include being uncircumcised, smoking, and having contact with carcinogens such as oil, tar, and/or arsenic. There is a link with the human papillomavirus, and the condition may be found after phototherapy for psoriasis. I have seen it in three patients followed up for more than 20 years for lichen sclerosus et atrophicus (LSA). It accounts for approximately 0.5% male malignancies in Western countries.

Symptoms often have been present for many years. Patients complain of itching, bleeding, irritation, and fore-skin problems, such as tethering and phimosis. Tumors may involve the glans penis in approximately 50% and prepuce in 20%, and in some patients both glans and prepuce are affected. There may be small nodules, nonhealing areas, and ulceration as well as phimosis and LSA. Palpable lymph nodes may be the first place for metastases. Referral to a urologist and specialist treatment center is needed. Diagnosis is by biopsy. Treatment is resection followed by radiotherapy and chemotherapy. Prognosis is poor.⁵

STDs

Although only a few complications of STDs could be considered to be emergencies, symptoms and signs suggestive of an STD should always be taken seriously. Accurate history taking and diagnosis or multiple diagnoses are necessary both for the purposes of effective therapy and appropriate partner notification (contact tracing), with follow-up to make sure the patient has been adequately cured. As the condition is infective, there is all the more reason why good diagnosis and treatment as a public health measure are imperatives. In many localities, there are also civil regulations that differ from country to country on treatment of STDs, aspects concerning confidentiality, their notification to public health authorities, and their situation within the legal framework of that country.

Here, concise guidelines are given for management of gonorrhea, genital tract infection with *C. trachomatis*, herpes genitalis, and syphilis, which may all have emergency elements in their presentations. These guidelines will generally follow those of the Clinical Effectiveness Group of British Association for Sexual Health.

Gonorrhea

Gonorrhea is an STD resulting from infection with *N. gonorrhoeae*, a gram-negative diplococcus. The primary sites of infection are the mucous membranes of the urethra (Figure 29.1), endocervix (Figure 29.2), rectum (Figure 29.3), pharynx (Figure 29.4), and conjunctiva. Transmission is by direct inoculation of infected secretions from one mucous membrane to another.⁶

In men, 80% have a mucopurulent urethral discharge and approximately 50% have dysuria if the urethra is infected. Most specialists will be only too aware of the man with acute gonorrhea entering the consulting room with a yellowish catarrhal urethral discharge. In a few, asymptomatic infection may occur. Pharyngeal infection is usually asymptomatic. Rectal infection in men who have sex with men (MSM) may be asymptomatic, but approximately 20% have anal discharge or perianal pain or discomfort.

In women, up to 50% with infection of the endocervix have no symptoms. Up to 50% may also have an increased vaginal discharge. If there is a degree of PID, lower abdominal pain may be found in up to 25%. Gonorrhea is also a rare cause of intermenstrual bleeding or menorrhagia. Twelve percent of women complain of dysuria but not frequency.



Figure 29.1 Urethral gonorrhea.

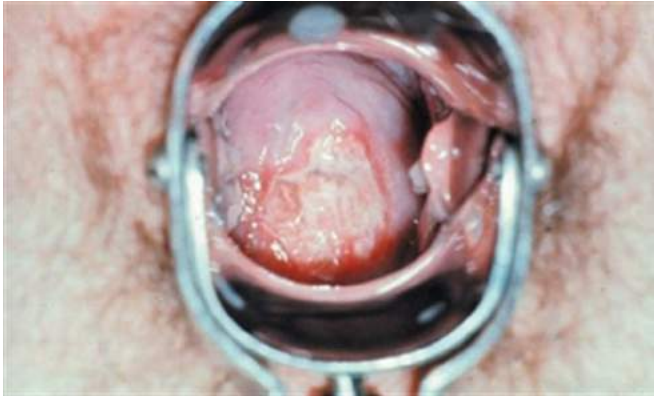


Figure 29.2 Purulent cervicitis in gonorrhea.



Figure 29.3 Anorectal gonorrhea.



Figure 29.4 Pharyngeal gonorrhea after fellatio.

Rectal infection may occur after anal sexual intercourse or by spread from genital secretions, as well as from saliva in anilingus. As with men, pharyngeal infection is usually asymptomatic.

It is important to realize that *N. gonorrhoeae* may coexist with *C. trachomatis*, *Trichomonas vaginalis*, and *Candida albicans*.

If signs are present at all, up to 50% may have an endocervical discharge, but there may be few positive signs, the patient either presenting as a sexual partner of a man infected or presenting for a genital diagnostic check. Complications are transluminal spread of *N. gonorrhoeae* from the urethra to involve the epididymis and prostate in men ($\leq 1\%$) and endometrium and pelvic organs (PID) in women, probably less than 10%. Hematogenous dissemination may also occur from infected mucous membranes (it is worth considering infection of the pharynx when this occurs), resulting in skin lesions, arthralgia, arthritis, and tenosynovitis. Disseminated gonococcal infection is uncommon, but in the 1960s outbreaks of gonococcal dermatitis arthritis syndrome were seen.⁷

Gonococcal Infection of the Eye

In adults, this infection is rare. It may occur from fomites but more likely as the result of sex play. The conjunctiva is swollen, red, edematous, and painful, and pus is pouring out. The possibility should always be considered that it was caught as a strain of penicillinase-producing *N. gonorrhoeae* and adequate cultures taken. It responds rapidly to appropriate antibiotics, and an ophthalmologic opinion should always be requested to exclude corneal ulceration.

In children, this infection is usually caught in places with poor hygiene, such as crowded tenements and refugee and nomad camps, but of course it may be after sexual interference with that child. Its appearance will be similar to that found in an adult.

Ophthalmia neonatorum in the United Kingdom is defined as a purulent discharge from the eyes of an infant within 21 days of birth. It is now much more common in babies infected with *C. trachomatis* than in those infected with *N. gonorrhoea*.

Diagnosis is made by identification of *N. gonorrhoeae* from an infected site. Microscopy with visualization of gram-negative diplococci is obviously the fastest way of making a presumptive diagnosis in men with symptomatic urethral gonorrhea, but in women microscopy from endocervical smears even with skilled technicians will pick up only approximately half the cases. Thus, cultures are also needed. Here again, specimens need to be adequately collected and selective culture medium containing antimicrobials are recommended to reduce contamination.⁸ Culture tests help very much in diagnosis of gonorrhea from the pharynx, cervix, and anorectal canal as well as the urethra, and are the only way to monitor sensitivity and resistance patterns to antimicrobials in gonorrhea.

Nucleic acid amplification tests (NAATs) and nucleic acid hybridization tests are more sensitive than cultures and can be used for screening urine samples and self-taken vaginal swabs. NAATs do not provide an organism for antimicrobial susceptibility testing, and false positivity is a challenge when testing for gonorrhoea in low prevalence situations.⁹ NAATs also offer the highest sensitivity for detection of oropharyngeal gonorrhoea.⁹ Confirmation, especially in medical-legal cases, still requires adequate culture sampling. NAATs also do not show sensitivity patterns for antimicrobials. Screening for coincident STDs should always be performed in patients with gonorrhea.

Treatment

Since the day penicillin was first used in its treatment, *N. gonorrhoeae* has shown the capacity to develop reduced sensitivity and resistance to many antimicrobials. For instance, resistance to penicillin, tetracyclines, and ciprofloxacin is common.¹⁰

Therapy should eliminate at least 95% of those presenting in the local community.¹¹

Generally, the following [treatment] will work unless resistance has developed:

- Ceftriaxone [500 mg intramuscularly as a single injection with azithromycin 1 g orally as a single dose]

[Alternative Treatment: Due to increasing worldwide gonococcal antimicrobial resistance, alternative regimes have exceptions to their efficacy.]

- [Cefixime 400 mg orally]
- Spectinomycin 2 g IM [Spectinomycin is not available in many countries.]

Azithromycin is not recommended for the treatment of gonorrhea due to reports of developing resistance to it.¹²

Coinfection with *C. trachomatis*

Between 20% and 40% of men and women with gonorrhea will also be infected with *C. trachomatis*, so often combined therapy for both *N. gonorrhoea* and *C. trachomatis* is given at the same time. Thus, for the latter, azithromycin 1 g PO or doxycycline 100 mg twice daily for 7 days is recommended. When prescribing antibiotics, care should always be taken in pregnant women, patients with known antibiotic sensitivities or allergies, patients who are taking other medications, and (in the case of doxycycline) patients exposed to sunlight.

Sexual Partners

Partner notification is needed. It is a skill that requires diplomacy, and the patient will often be helped by a professional health adviser. Sexual partners should be treated for gonorrhea, preferably after evaluation as for STI.

Genital Tract Infection with *C. trachomatis*

This is the most common nonviral STD found in industrialized countries. It is thought that 5%–10% of sexually active women younger than 24 years and men in their late teens and early twenties may be currently infected.¹³ Risk factors are being a young adult, having a new sexual partner in the last year, and



Figure 29.6 Chlamydial ophthalmia in an infant.

lack of consistent use of condoms. There has been a pattern of serial monogamy. Although it usually causes a mild urethral discharge in men with variable dysuria (Figure 29.5), there may be few adequate symptoms in some men, and it is frequently asymptomatic in women. In women, when there are symptoms, they are variable and may include postcoital or intermenstrual bleeding, lower abdominal pain, purulent vaginal discharge, mucopurulent cervicitis, and dysuria. Babies may be infected from mothers via the birth process (Figure 29.6). In men and women, after anal sexual intercourse there may be a proctitis with anal discharge and anorectal discomfort. It is the complications that will cause the patient to seek help as an emergency.

Pelvic Inflammatory Disease

PID results when infections ascend from the cervix or vagina into the upper genital tract.¹⁴ It includes endometritis, salpingitis, tuboovarian abscesses, and pelvic peritonitis. The main causes are *C. trachomatis* and *N. gonorrhoeae*, but *M. hominis* and anaerobes are also found. Even after laparoscopy, no bacterial cause may still be found.

Lower abdominal pain is the most common symptom, with increased vaginal discharge, irregular bleeding, deep dyspareunia, and dysuria also present in some women. The cervix may have a mucopurulent discharge with contact bleeding, indicative of a cervicitis. Adnexal and cervical motion tenderness on bimanual examination is the most common sign, but pyrexia and a palpable adnexal mass may also be present.

Diagnosis

Laparoscopy with microbiologic specimens from the upper and lower genital tracts is considered the gold standard for diagnosis, but this is not always available. If laparoscopy is not available, the presence of lower abdominal pain, increased vaginal discharge, cervical motion, and adnexal tenderness on bimanual examination, together with confirmatory subsequent diagnosis from swabs taken from the lower genital tract, will give a diagnosis but only with a specificity of approximately 70%.

Treatment of PID

Prompt diagnosis and early treatment should reduce the risk of tubal damage and should be started before microbiology results are known. Regimens should cover all bacterial causes and may need to be given IV for the first few days.



Figure 29.5 Chlamydial urethritis with molluscum contagiosum.

A suitable regimen would be ceftriaxone 2 g IM plus doxycycline 100 mg twice daily or ofloxacin 400 mg twice daily plus metronidazole 400 mg twice daily for 14 days. Appropriate analgesia should be given. Partner notification is essential to prevent reinfection.

Other complications of genital *C. trachomatis* infection include Fitz-Hugh-Curtis syndrome (perihepatitis), transmission to the neonate (neonatal conjunctivitis, pneumonia), epididymo-orchitis, adult conjunctivitis, and sexually acquired reactive arthritis (SARA)/Reiter syndrome (more common in men). Of the complications mentioned, both epididymo-orchitis and SARA may present as emergencies and are discussed here.

Epididymo-Orchitis

An acute epididymitis may occur in older men (generally at least 35 years old) due to urinary tract infection usually caused by coliform organisms, although age does not preclude sexual activity and sexually transmitted causes of epididymitis should always be considered if there is an active sex life. In younger men under age 35, more frequently *C. trachomatis* and less frequently *N. gonorrhoeae* are the cause, although urinary tract infection, especially if there are underlying genital tract anomalies, should be considered. Rarer causes, but those still found in developing countries, are tuberculosis and leprosy. Mumps, especially where there are many youngsters living closely together, also should be considered. The differential diagnosis from torsion of the testicle has already been described. There does need to be a planned approach in centers where the symptomatic patient may well get to a venereal disease clinic but the asymptomatic patient gets to a urologist. Treatment includes excluding a urinary tract infection, giving necessary analgesics and scrotal support, and administering appropriate antibiotic therapy for either *N. gonorrhoeae* or *C. trachomatis* (in the latter case doxycycline 100 mg twice daily for 14 days). Partner notification for STD causes of epididymo-orchitis is a requisite.

If any group of young men presenting with epididymo-orchitis is analyzed, annually, there will be one or two who do not have an epididymo-orchitis but have, in fact, a malignant tumor of the testicle. The skilled clinician usually develops a sixth sense, and a high index of suspicion is needed for these cases when not presenting to a urologist. In my practice malignant tumors of the testicle are also more common in men with HIV infection. The usual signs of testicular cancer include a lump in the testicle, painless swelling, or altered consistency of the testis; any of these may be found on a medical examination. Ultrasound and nuclear magnetic resonance help in the diagnosis, and the patient needs to be seen rapidly by the appropriate team in a center that has specialist knowledge of testicular tumor management.

SARA/Reactive Arthritis Syndrome

SARA/reactive arthritis syndrome, previously known as Reiter syndrome, has been included as an emergency, as it may well have an insidious onset that can present to a variety of clinicians. It is often missed in its early stages; in practice, less would be seen if more often the early diagnosis of *C. trachomatis* (often asymptomatic in young men) was considered and appropriate therapy (best given as azithromycin 1 g PO) was instituted. Missing SARA may have disastrous effects in sportsmen with active sex lives, when damages to the hip, knee, ankle, and small joints of the foot, as well as tenosynovitis, are short- and long-term side effects.

Circinate balanitis (Figure 29.7) may well occur a few weeks before other major symptoms and should act as a trigger



Figure 29.7 Circinate balanitis.

for the dermatologist to screen for STDs (especially *C. trachomatis*) and to give appropriate antibiotic therapy with doxycycline or azithromycin. As any mucosa may well be affected, there is a need to look further than the genitals. Conjunctivitis occurs in approximately 30% of cases in the early stages as well as usually mild oral and buccal lesions in early SARA. In chronic SARA obviously the well-known classical signs of chronic arthritis, serious skin lesions, keratoderma blennorrhagica, onycholysis, and eye complications (such as an anterior uveitis) are all known but are not part of emergency presentation. The condition is far from common in women, but a vulvitis may occasionally present. When considering the consequences and the differential diagnosis of *C. trachomatis* genital infection, it is necessary to consider the much more common and very frequently seen uncomplicated *C. trachomatis* genital infection.

Diagnosis and Treatment of *C. trachomatis* Genital Infection

Diagnostic tests are changing rapidly for *C. trachomatis*.¹³ The tests for standard of care are NAATs. These are more sensitive and specific than enzyme immunoassays (EIAs). Suboptimal EIAs are no longer appropriate. No test, be it NAAT or EIA, is 100% sensitive or specific. The field of diagnosis changes so rapidly that ongoing specialist advice should be considered by those whose main specialty is not STDs.

[NAAT's samples from other than urethra or cervix where clinically indicated may be taken from rectal, pharyngeal, and conjunctival specimens in men or women; in the absence of culture tests, however, NAATs are usually taken from these sites.]

In Europe, in the last 5 years rectal lymphogranuloma venereum (LGV) has been seen not infrequently in MSM, and British guidelines recommend that when a rectal NAAT is found to be positive, it is sent for further testing for LGV typing to the appropriate laboratory. Rectal LGV was in recent years first seen in the Netherlands occurring in MSM who had passive anal sex without the use of a condom for protection against STIs. Since then, it has been found in MSM throughout Western Europe. The most common sign is a proctitis that may be not only purulent but bloody. There may be considerable alteration of bowel habits, perhaps being mistaken for irritable bowel syndrome, ulcerative colitis, or Crohn disease. There may be a fever, a general feeling of malaise, and inguinal regional lymphadenopathy. In contrast, there may be few symptoms. As would be expected, it may be found with other STIs in this region—namely, syphilis,

rectal gonorrhea, anorectal herpetic infection, anal condyloma acuminata, HIV infection, and hepatitis B and C—all of which should be investigated in this group of patients.

Treatment of Uncomplicated Genital *C. Trachomatis* Infection

Recommended treatment includes doxycycline 100 mg twice daily for 7 days, ofloxacin 200 mg twice a day for 7 days, or azithromycin 1 g PO, the latter being recommended by the World Health Organization for pregnant women but not completely passed as being safe by all national health agencies, although it probably is.¹⁵

Herpes Genitalis

As this condition is so often not only painful but comes as a most unpleasant shock to self-esteem in a world where young people are so media aware, it is the STD that most often gets the venereologist called outside his normal working day (Figures 29.8 and 29.9). Over the years, it is often the parent of young persons who has realized that they are suffering from genital herpes who calls so often at weekends and public holidays.



Figure 29.8 Painful ulcer on penis, syphilis excluded, but herpes simplex virus type 2 isolated.



Figure 29.9 Acute herpes genitalis in a woman.

Etiology

The two forms are herpes simplex virus type 1 (HSV-1), the usual cause of orolabial herpes and herpes simplex virus type 2 (HSV-2).

Natural History: What Do We Know about Herpes Genitalis?

Infection may be primary or nonprimary. Disease episodes may be initial or recurrent and symptomatic or asymptomatic. Prior infection with HSV-1 modifies the clinical manifestations of first infection by HSV-2. After childhood, symptomatic primary infection with HSV-1 is equally likely to be acquired in the genital or oral areas.

Following primary infection, the virus becomes latent in local sensory ganglia, periodically reactivating to cause symptomatic lesions or asymptomatic (but infectious) viral shedding.

New diagnoses of genital herpes are equally likely to be caused by HSV-1 or HSV-2; the median recurrence rate, after a symptomatic first episode, however, is 0.34 recurrences per month for HSV-2 and 0.08 recurrences per month for HSV-1. Recurrence rates decline over time in most individuals, although the pattern is variable.

The majority of individuals found to have asymptomatic HSV-2 infections subsequently develop symptomatic lesions. Asymptomatic perianal HSV shedding in HIV-negative HSV-2-seropositive MSM is common.¹⁶ In HIV HSV-2-seropositive men, both symptomatic and asymptomatic shedding are increased, especially in men with low CD4 counts and in men who are also seropositive for HSV-1.¹⁷

As most modern information is available on the Internet, no wonder patients, their families, and friends get upset when herpes genitalis is considered. So what are the clinical features, including ones that could be considered an emergency? In both sexes, there is painful genital ulceration often with local dysuria and urethral or vaginal discharge. There may be fever and myalgia. Unpleasant symptoms are more common in primary infection. Some patients are asymptomatic. Genital ulceration begins with an itchy vesicle that breaks down to form a shallow superficial painful ulcer, often in groups, on the genitals or cervix or in the anorectal canal (often very painful indeed). Complications include autonomic neuropathy resulting in retention of urine and aseptic meningitis.

Confirmation of Diagnosis

It is necessary but often difficult to isolate HSV from genital lesions. Successful diagnosis depends on using swabs taken directly from the base of the lesion, maintaining the cold chain (4°C), rapidly transporting specimens to the laboratory, and avoiding freeze-thaw cycles.

Serology

Most commercial tests for HSV antibodies are not type specific and are of no value in the management of genital herpes. Type-specific EIAs based on glycoprotein G (gG1, gG2) or Western blot assays are becoming available. Type-specific immune responses can take 8–12 weeks to develop following primary infection. It is now becoming possible for serologic evaluation of genital herpes, but that needs access to both HSV-1 and HSV-2 type-specific assays. Caution is needed in interpreting results because even highly sensitive and specific assays have poor predictive values in low-prevalence populations.

The clinical utility of these tests has not been fully assessed. Virus detection remains the method of choice, but

serologic evaluation tests may be useful for the following conditions:

- Recurrent genital ulceration of unknown cause
- Counselling patients with initial episodes of disease
- Investigating asymptomatic partners of patients with genital herpes
- Evaluating genital herpes in pregnancy

Management of Genital Herpes and Its Complications

First Episode of Genital Herpes

The faster oral antiviral drugs are given preferably within hours of lesions forming. Acyclovir, valacyclovir, and famciclovir all reduce the severity and duration of episodes. The availability of these drugs depends on local conditions. Manufacturers' recommendations regarding dosage should be followed. Antiviral therapy does not alter the natural history of the disease. Topical agents are less effective than oral ones. IV therapy is only indicated when the patient cannot swallow or tolerate oral medication because of vomiting. In addition, local bathing with normal saline solution and analgesia helps. Some clinicians recommend topical anesthetic agents, but then there is the danger of potential sensitization.

Regimens recommended for adults (all for 5 days) are acyclovir 400 mg three times a day, famciclovir 250 mg three times a day, or valacyclovir 500 mg twice daily.

Management of Complications

Hospitalization may be needed for urinary retention, meningism, and severe constitutional symptoms. If catheterization is needed, suprapubic catheterization is preferred because it prevents the risk of ascending infection and allows normal micturition to be restored without multiple removals and recatheterizations. Always, however, try sitting the patient in a warm bath and allowing him or her to try to pass urine in it before catheterization is attempted. It often works.

HIV-Positive Patients

In the early days of HIV, especially when dealing with gay men before the advent of highly active antiretroviral therapy (HAART), when often enormous painful and distressing perianal herpes was found, resistance of HSV to antivirals was found. With HAART, however, this condition is far less frequently seen.

Recurrent Genital Herpes

Although causing much personal distress to some patients, genital herpes cannot really be considered as an emergency. Most recurrences are self-limiting, but a good doctor-patient relationship can be supportive for the patient. Strategies for treatment include general support, treatment with antivirals episodically, and suppressive therapy. All of these management techniques need working out for each individual patient.

Management of Genital Herpes in Pregnancy

Guidelines for genital herpes in pregnancy are categorized into management of first episodes and recurrent episodes. Accurate clinical classification is difficult. Viral isolation and typing and the testing of paired sera (if a booking specimen is available) may be helpful. There are guidelines for management depending on when genital herpes was first acquired and in what trimester.¹⁸ Basically, all guidelines suggest continuous acyclovir

in the last 4 weeks of pregnancy and an elective cesarean section despite lack of evidence for its effectiveness. The risks of vaginal delivery for the fetus are small and must be set against the risks to the mother of cesarean section.¹⁹

Syphilis

In this section, some of the pitfalls (mistakes) in making a diagnosis and some of the side effects that may occur in treatment are discussed. There are several good descriptions of syphilis in many dermatology and venereology textbooks that can be used for reference.

It was once said, "Always consider syphilis" (Sir William Osler, 1909). That may well be almost as true now, but also add on HIV infection. There are three main reasons why syphilis is missed:

1. The patient does not know about it or fails to ask for medical advice.
2. The clinician (and this is far more serious) does not consider it in the differential diagnosis.
3. Public health authorities do not stress its importance. For the last 30 years, the focus has been on HIV disease as the number one STI to consider.

Like much of medicine, a good history will consider syphilis. Always take a sexual history in a quiet place out of the earshot of others. Let the patient know that you will keep confidences and be discreet. Do not show any surprise at what you are told; all things human are within the knowledge of a good clinician. Be candid and ask if the patient is not forthcoming about his or her sexual practices. Start with simple questions, such as "Was a condom used?" If the patient is a man, find out if he had sex with another man, a woman, or both sexes (if that has not already been proffered). There has been a rise in homosexually (Figure 29.10) contracted early primary and secondary syphilis in MSM in Europe, North America, and parts of East Asia, often with HIV infection and pharyngeal and rectal gonorrhea. Early syphilis remains common in Eastern Europe in heterosexuals and has been seen in pockets all over Western Europe, often in groups related to street drugs and/or prostitution (where sex workers are brought in from Eastern Europe). Syphilis is no respecter of social position, and perhaps



Figure 29.10 Anal chancre.

the more money a person has the easier it is to travel and meet others for sexual purposes. Always consider any genital sore to be syphilis until proven otherwise (herpes genitalis is much more common), and always consider syphilis in the differential diagnosis of eruptions. Remember that most dermatology textbooks in industrialized countries have used as photographs white skins; presentation in brown, yellow, or black skins may look different. The eruption may last for weeks but may be fleeting and disappear before the patient has had a chance to see a physician if the appointment is delayed. Remember that the patient with secondary syphilis may feel unwell, be running a fever, or even be jaundiced. Secondary syphilis (Figures 29.11 and 29.12) may present with many different signs, some of



Figure 29.11 Secondary syphilis.



Figure 29.12 Secondary syphilis, palms.

them rare: meningism, uveitis, deafness, arthralgia, periostitis, as well as skin signs easily missed such as alopecia, snail track ulcers (buccal mucosal patches), and condyloma lata around the mouth, axillae, inguinal regions, and anus and toe webs. Generally, unless the patient is severely immunocompromised, standard serologic tests for syphilis will be reactive in secondary syphilis.

Diagnosis of Primary Syphilis

The ulcer (chancre) is said to be painless with rolled indurated edges but, like many classical descriptions, this is not always so. If the patient has applied antiseptic lotion or cream or has taken an antibiotic such as penicillin, tetracycline, or erythromycin prior to being seen, dark-field examination for *Treponema pallidum* is a waste of time, as it will not be found. Dark-field examination for *T. pallidum* by a skilled observer when the chancre has not been modified is still an effective way of making a fast diagnosis, but it requires skill and much practice and is time consuming. Serologic tests for syphilis need to be performed. If there is any doubt about syphilis, they need to be repeated at 1 month and 3 months. The initial test is likely to be an EIA; if reactive, the Venereal Disease Research Laboratory test or rapid plasma reagin test, *T. pallidum* hemagglutination test, and fluorescent treponemal antibody absorption (FTA-ABS) test should be performed. It has to be remembered that, in the early stages of syphilis, there may be only *T. pallidum* seen on dark-field microscopy. One of the first blood tests to become reactive is FTA-ABS at about 2 weeks.

Remember that it may be difficult to tell if the patient has had either syphilis or a nonvenereal treponematoses (such as yaws or pinta) treated in the past, whether or not serologic tests refer to the present or past infection. If in doubt, it is best to treat again.

Treatment

In parts of the world where there are good public health facilities staffed by specialists for the treatment of STDs, syphilis is best treated in such facilities; in other parts of the world, however, the dermatovenereologist will be responsible for treatment.

For early syphilis that is primary, secondary, or early latent, the following treatment is recommended: either benzathine benzylpenicillin 2.4 million units IM or procaine penicillin 0.6 million units IM daily for 10 days. If the patient is allergic to penicillin, doxycycline 100 mg twice daily for 14 days is recommended. The patient should be seen after a week to make sure that he or she is taking prescribed medication. *T. pallidum* is highly susceptible to penicillin—not requiring a high level, but rather a prolonged level of penicillin in tissues for it to be bactericidal, as penicillin only acts on dividing cells. Studies on doxycycline, tetracycline, erythromycin, azithromycin, and ceftriaxone all show efficacy in syphilis, but often the trials have been in the past and not conducted to modern criteria. There have also been reports of resistance to azithromycin, so it cannot be recommended.

ANTIBIOTIC THERAPY AND SIDE EFFECTS

Acute Anaphylaxis after Treatment with Penicillin

This side effect is rare, and no patient should be given penicillin if there is any history of allergy to it. Desensitization takes time and is inappropriate in a busy clinic. Staff should be trained in resuscitation, and there should be the drugs and equipment

present to give emergency treatment for acute anaphylaxis as well as the ability to summon immediate aid from resuscitation emergency services.

Jarisch-Herxheimer Reaction

This reaction occurs in more than half of patients when penicillin is given for early treatment of syphilis. Within 8 hours of an injection, the patient notices a febrile illness with malaise, headache, chills, and rigors. It clears quickly, but the patient should be told about it beforehand that it is not an allergic reaction. It is thought to be due to release of lymphokines including tumor necrosis factor and interleukins. In late syphilis, although rare, it may be potentially life threatening, so steroid cover is given for 3 days before treatment.

Procaine Reaction

This reaction will become rarer the more often benzathine benzylpenicillin is used instead of procaine penicillin. It is more common in men and is a sort of anaphylactoid reaction. The patient experiences auditory symptoms, a fear of impending death, seizures, and a violent behavioral reaction. It is thought to be due to inadvertent IV administration. It is much less common than it was 50 years ago when procaine penicillin was the treatment for gonorrhea. Most of the patients recovered without any therapy, although it usually needed all the clinic staff to hold the patients down in their struggles.

Stevens–Johnson Syndrome

Again, this has become infrequent in the treatment of STDs, because the use of sulfonamides (especially the long-acting ones) and cotrimoxazole has declined in the day-to-day treatment of conditions presenting in clinics. It is still seen, however, in the treatment of HIV disease after the use of nonnucleoside reverse transcriptase inhibitors such as nevirapine.

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Emergency management of environmental skin disorders: Heat, cold, ultraviolet light injuries

Larry E. Millikan

Environmental skin disorders usually are associated with ambient changes (heat, humidity, and intensity of ultraviolet [UV] solar rays) and new environments (ski slopes, beaches, jungles/rain forests, and areas with exotic animals unfamiliar to patients). Many of these new surroundings cause unique dermatologic reactions familiar to natives who understand the need for avoidance but unfamiliar to others who must seek dermatologic care. In fact, travel-associated dermatoses are responsible for one out of five diseases in travelers.¹

PROPER AND EARLY MANAGEMENT

Proper and early management of skin disorders due to environmental factors might avert the ruin of a long-anticipated trip or vacation. In some instances, the environmental exposure occurs at home before departure and then is manifested during travel to or at the destination. Such environmental exposures from contact allergens, toxins, and infections or infestations can be delayed. As a result, clinical manifestations are also delayed and may not appear until several days after the return home; hence, a history of recent travel is essential to exclude an exposure that may have occurred in the home environment. The challenge of many of the environmentally associated emergencies is to initiate therapy early, to achieve the best possible outcome, and, in some infectious complications, to be able to institute the now-delayed therapy to avoid greater increases in morbidity and mortality.

HEAT EMERGENCIES

These emergencies are largely associated with ecotourism, where the traveler is truly out in the environment—a marked departure from the usual life in “civilization” with its air-conditioned environment, dehumidification, and general protection from extremes.¹ These exposures, coupled with the “holiday” conditions of food and beverage excess (i.e., alcohol), and possibly more than usual physical activity could impair the body’s ability to maintain homeostasis, and in extremes, the regulation of body core temperature is lost. The resultant elevation of core temperature can reach a potentially fatal level, where immediate care may be life saving. Simple measures—rehydration, cool water immersion, ice packs, and limiting of activities—are essential. Newer approaches (electrolyte replacement fluids and some drugs) reported in Olympic and world-class sports may be the prevention as well as treatment in the future.² As these conditions occur largely in primitive/remote areas, where access to professional assistance is limited, if available at all, anticipation of heat stress is the primary step

to avoid the serious sequelae (coagulopathy, etc.).³ Obviously, these scenarios are not the domain of the dermatologist, but one should be aware of risk to encourage the patient to be alert to the symptoms and signs and to seek appropriate care, should they appear.

UV LIGHT

Here again, the key is environmental change. Essentials to anticipate include the enhanced UV exposure closer to the tropics and the effect of altitude on intensity of UV, especially with a pale, light-skinned traveler seeking respite from winter. The temptation of the sun during the long dark days is often too great, and careful planning and prevention are ignored or forgotten. Lower latitudes and higher altitudes are key to risk in the environment, as each enhances the intensity. The higher altitudes have thinner air filtering and less of the incoming sunlight, whereas the nearer the equator, the greater is the direct effect of the rays. An essential aspect is education in the use of sunscreens prior to departure and gradual increase of exposure to induce melanin formation.

Additionally, the present world of polypharmacy has greatly expanded the list of photosensitizing drugs, particularly for hypertensive and/or diabetic patients. The prototype in the past has been the group of furocoumarins and the sulfa-related drugs (Figure 30.1). Whereas the former group were used therapeutically, the latter are omnipresent in the treatment of infections, diabetes, and hypertension (diuretics) (Figure 30.2). The traveler should be aware of any drugs taken with such potential and use extra care. The personal physician and the pharmacist should be the best source for this information and obtain it before the patient travels. Many busy family practitioners may not have the most recent information, whereas the pharmacist will usually be able to readily access this information.⁴

Modern sunscreens are the real answer.⁵ Newer guidelines for protection (sun protection factor [SPF]) are often confusing, as to need of repeated application of the agent and the SPF number. Generally, an SPF over 30 is appropriate.

UVA protection is essential for the informed and concerned consumer. The significance of UVA grows as data accumulate in its role in carcinogenesis, a far more insidious and significant “thief in the night” due to its much less obvious impact without the “sunburn” that inspires caution with UVB.⁶ The significance of UVA relates to its greater penetration into the dermis (whereas UVB only penetrates superficially) and the immunosuppression it can cause. This problem is not emergent/acute, but it is the cumulative exposure that is the major cause/factor in the carcinogenesis. The acute problems are less



Figure 30.1 Phototoxic reaction to a topical antimicrobial.



Figure 30.2 Sulfonamide-associated photoreaction.

associated with the risk for carcinogenesis; the immediate discomfort is the primary reason for the need for sunscreens.

The early agents were effective protection but not aesthetically desirable and hence not well accepted. These agents included Red Vet Pet (red veterinary petrolatum), which had very good sunscreensing properties and hence was standard in water survival kits, when I was a flight surgeon in the U.S. Navy. Sudden loss of your ship put you on the open ocean in a life raft (if you were lucky) but often exposed to intense sunlight and sunburn. In this scenario, it could be life saving, and the greasy aspects of petrolatum were not a great concern—much different from applying it while on the sandy beach or by the pool. The total blockers, such as titanium and zinc oxide, have many, if the same, problems and are used primarily in medical conditions of severe photosensitivity.

The first chemicals, other than physical sunscreens such as *para*-aminobenzoic acid, were primarily protective against UVB (and the sunburn sequelae), as that was the easiest to measure with SPF testing. It represented our best knowledge of the situation at the time. Of course, important prevention from UVB sunburn is the acute concern and would be key to avoid acute problems for the traveler. Much of the literature on



Figure 30.3 Irregular pigmentation after uneven application of a sunscreen.

sunscreens to date has dealt with UVB protection preventing sunburn, but it now is appreciated that the deeper penetration of the UVA rays into the dermis greatly enhances risk for carcinogenesis but poses a lesser risk for sunburn.

Additional agents, such as avobenzone (Parsol 1789), one of the first with UVA screening, are now preferred due to their broader-spectrum A/B effect. They have greater acceptance but, in all instances, need to be used expectantly to prevent future acute episodes. This field has rapidly changed with the newer agents Helioplex®, Tinosorb M®, and Mexoryl XL®, which are just a few examples of this developing field. Even and repeat application is essential for protection, and the effectiveness is seen in Figure 30.3. The irregular tanning attests to protection potential. The potential for photoreactions with many of the marketed agents has led to a renewed interest in the natural sunscreens.⁷

Total disregard for usual “sun sense” can produce an emergency situation, especially when the results are near-second-degree burns, enhanced risk for infection, and significant morbidity. Acute treatment is instituted to prevent usual burn complications, fluid loss, infection, and systemic sequelae. Oral steroids will be of assistance in the first few hours, and non-steroidal antiinflammatory drugs may be helpful in stopping the progression. These are primarily administered orally, but some newer preparations and concentrations of diclofenac gel are showing promise.⁸

CONTACT DERMATITIS

There are several groups of plants causing type 4 reactions that can be encountered, and most are widespread, if not worldwide, in distribution. The *Compositae* group of plants is the most widespread, but fortunately only a few persons have allergic potential, and these are ones with extensive exposure, usually occupational, floriculture, and/or agriculture. The hallmark of the group is the daisy-like composite flower; the group also includes some popular herbal sources such as echinacea.

Even the common dandelion is in the same group. It is a vast group found everywhere, so they are difficult to avoid. The sesquiterpene lactones are the common antigens, and it has been recently documented with a higher incidence in children (4.2%) and adolescents (2.6%), primarily in those who are atopic.⁸ This allergy further increases the risk, as atopic children are those with greatest morbidity in tropical dermatology from impetiginization and secondarily infected miliaria, seeming to double the risk for such children in the tropics.

The Rhus/Toxicodendron group has a much higher incidence of allergy but fortunately has a smaller range of distribution. There is a classic paper that documents related plants that result in worldwide exposure—the very sensitive subject commences extensive travel, arrives in the tropics, and gets a perioral contact dermatitis from eating mango. Then, on to the Pacific Rim, where dermatitis on the buttocks develops from toilet seats finished with lacquer (the related Japanese lacquer tree as the source). In India, a dermatitis on the neck occurs from laundry ink in the collar (the Indian marking nut tree). The different species have definite and limited range, but the oleoresin cross-reacts, and sensitivity then can even be widespread. Even cashews are related, but fortunately the usual processing inactivates the allergen.⁹ Although frequently presenting as simple vesicles in a linear display (Figure 30.4), this allergen also can result in the most dramatic vesicular and vesiculobullous reactions that can be widespread and are a frequent site for impetiginization. Such secondary infection is the most frequent reason for emergency care, as it progresses (i.e., erysipelas and with certain nephritogenic streptococci symptomatic renal disease). Exposure to contact dermatitis can be initiated even before departure or while on the trip. Either way, the morbidity can be such that it can nearly ruin the vacation/trip.

Alstroemeria is a newer problem largely due to the popularity of the plants in the flower and greenhouse industry. Although previously limited in range, the artificial nature of growth in the trade has greatly increased the exposure for persons in the business of floriculture. Previous sensitization and subsequent reexposure usually in the wild (primarily southern hemisphere) can give the same scenario as in the preceding paragraph in the seriously allergic individual. Primula sensitivity seems to be largely limited to the United Kingdom, where gardeners and floriculturists may develop the dermatitis.



Figure 30.4 Classic presentation of Rhus dermatitis.

The limited range of this group of plant species in cooler climates lessens the exposure to *primulin*, with the cool environment usually resulting in clothing that limits the amount of exposed skin. Similar complications seen with other allergic contact dermatitis reactions are still possible.

The usual clinical presentation with all of the previously mentioned allergens is so similar that often careful history taking, and even patch testing, may be necessary to detect the source of the contact dermatitis. Identification is essential to both educate the patient and prevent future exposure.

BEACH AND REEF: AQUATIC EXPOSURES

There are a few significant aquatic exposures that one can encounter; fortunately, most of the areas involved are well equipped to handle the problems as the shore, surf, and the coral reefs are primarily developed as resort facilities with all the amenities, medical included. The reefs are associated with many fish having toxic spine, such as the scorpionfish (Figure 30.5).

The “aquatourists” also are usually well educated in risk, emergency care, and first aid—all part of the basic exposure to water safety, scuba diving, surfboarding safety, and, in some areas, the swimming education program. Perhaps, the primary impetus is the periodic headline on shark attacks. Although these large fish get the headlines, the smaller creatures—seemingly innocents such as jellyfish—are the real cause of most problems.

Among coelenterates, two have the greatest impact. In the Western hemisphere, the Portuguese Man-of-War (*Physalia physalis*) is a cause of reported deaths. The long tentacles of this creature can break off, and the unsuspecting swimmer suffers the consequences of the contact and subsequent reaction from the multiple nematocyst toxicity. This usually happens to swimmers with lack of knowledge of the problem; they develop extensive stings and improper care (by freshwater exposure, massage, and other amateur first aid remedies), which results in continued “firing” of the nematocysts deposited in the characteristic linear arrays (Figure 30.6). The resort staff are usually available to assist. When managing these patients, it is also important to realize that broken tentacles can maintain toxicity for months, allowing for exposure over a broader window of time. The nematocysts, deposited in the patient’s dermis, are capable of firing off for variable periods of time after emergent



Figure 30.5 Local reaction from toxins in spines of a scorpionfish.



Figure 30.6 Linear reaction to nematocysts.

care has been completed, sometimes a cause for morbidity in some patients.

In Southeast Asia, a much more serious threat is *Chironex fleckeri* (also occasionally reported in the Caribbean, but most often from Australia). It is estimated that the fatality rate is between 15% and 20%.

The beaches in Australia (Queensland) have jugs of alcohol or vinegar strategically placed to provide emergency neutralization of the nematocysts—a potentially life-saving maneuver. Alternatively, experienced swimmers carry meat tenderizer as another approach to minimize morbidity. These creatures, colloquially sea nettles and sea wasps, are appropriately named.

The other headliner in this environment is the “deadly” cone shells. Possibly, the 15%–20% fatality rate might be diminished by education. These attractive shells are sought by collectors in Australia, California, and Florida, often by occasional collectors unaware of the risk. With education on precautions (gloves, etc.), emergency symptoms from the neurotoxin should be avoided. Definitive treatment is still not standardized.

The unusual nature of the venom has sparked interest in utilizing it therapeutically and developing better therapeutic avenues.¹⁰

CONCLUSIONS

Many other dermatoses have been described, from coral dermatitis to sea bather’s eruption, which are acute, usually minor, and rarely prompt a visit to the emergency room. There are a useful small atlas¹¹ and a definitive review¹² that can aid in approaching the dermatologic significance of these clinical challenges.

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Endocrinologic emergencies in dermatology

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Endocrine and metabolic diseases, besides affecting other organs, can result in changes in cutaneous function and morphology and can lead to a complex symptomatology. Dermatologists may see some of these skin lesions first, either before the endocrinologist, or even after the internist or specialist has missed the right diagnosis. Because some skin lesions might reflect a life-threatening endocrine or metabolic disorder, identifying the underlying disorder is important, so that patients can receive corrective rather than symptomatic treatment.

In this chapter, we review a few endocrine and metabolic disorders in which patients may present to the dermatologist with various skin lesions and in which the diagnosis of the underlying condition must be made in a timely fashion before the patient ends up with complications that could be fatal.

HYPERPIGMENTATION AND ADDISON DISEASE

Addison disease, or primary adrenal insufficiency, can be caused by either infiltrative disorders that invade the adrenal cortex or by destructive disorders that attack the adrenal cells. In either etiology, the adrenal cortex is unable to produce and secrete adequate amounts of glucocorticoid and mineralocorticoid hormones. The most common etiology of Addison disease used to be tuberculous granulomatous disease, but with declining infection rates in the developed world, the most common cause of Addison disease today is autoimmune destruction of the adrenal glands. Other less common causes of Addison include additional granulomatous fungal infections (histoplasmosis, coccidiomycosis), metastatic carcinoma infiltration of the adrenals, or bilateral adrenal hemorrhage.¹ Rarely, autoimmune Addison disease can be seen in association with certain inherited autoimmune polyglandular syndromes.

Clinical Features

The hallmark dermatologic feature of Addison disease is a darkening of the skin, particularly in sun-exposed areas (Figure 31.1). The hyperpigmentation of Addison disease is due to the melanocyte-stimulating activity of the high plasma levels of adrenocorticotrophic hormone (ACTH).² This skin darkening may be homogeneous or blotchy and is observed in all racial groups, although it can be more difficult to see in darker-skinned individuals. Also seen is significant increased pigmentation in the palmar creases, the vermillion border of the lips, flexural areas, in recent scars, and in areas of friction such as trouser waistlines. Mucous membranes, such as the buccal, periodontal, and vaginal mucosa, may show patchy areas of increased pigmentation. Women may have diminished axillary and pubic hair, as their androgen production occurs primarily in the adrenal glands.^{3,4} Patients with autoimmune Addison

disease may also present with vitiligo or alopecia areata, from a similar autoimmune destruction of melanocytes and hair follicles, respectively.

Diagnosis

Diagnosis should be based on clinical presentation confirmed by laboratory testing. The presentation of a patient with chronic primary adrenal insufficiency is that of long-standing vague symptoms, such as malaise, anorexia, joint aches, nausea, and fatigue, in addition to the skin findings mentioned earlier. Patients may also report craving high-salt foods.¹ The acute presentation of adrenal insufficiency is that of orthostatic hypotension, confusion, circulatory collapse, and abdominal pain. This acute presentation is frequently precipitated by an acute infection.

Biochemical testing to confirm the diagnosis is done with a cosyntropin (synthetic ACTH) stimulation test. In this test, serum cortisol is measured immediately prior to and 60 minutes following injection of 250 µg of cosyntropin. A cortisol level at 60 minutes of 18–20 µg/dL or greater is considered a normal adrenal response. If the serum cortisol at 60 minutes is less than 18–20 µg/dL, the patient is diagnosed with adrenal insufficiency; however, this may be primary or secondary (pituitary/hypothalamic mediated).⁵ Plasma ACTH should then be measured. In Addison disease (primary adrenal insufficiency), the ACTH will be elevated (>100 pg/mL) whereas in secondary adrenal insufficiency, the ACTH will be normal to low.⁵ Other biochemical findings supporting a diagnosis of Addison disease include hyperkalemia, elevated renin activity, hyponatremia, hypoglycemia, and hyperchloremic metabolic acidosis. Measurement of a morning plasma cortisol is sometimes done instead of a cosyntropin stimulation test, as a morning serum cortisol greater than 18–20 µg/dL rules out the diagnosis of adrenal insufficiency and a value of less than 3 µg/dL makes it very likely. In many patients, serum cortisol falls within the intermediate range and further testing is required, making cosyntropin stimulation the preferred testing method for diagnosis.⁵

Treatment

Treatment of Addison disease includes replacing both glucocorticoids and mineralocorticoids. Typical dosing of glucocorticoids is prednisone 5–7.5 mg daily or hydrocortisone 15–20 mg in the morning and 5–10 mg in the evening. For mineralocorticoid replacement, fludrocortisone is given at a dose of 0.05–0.3 mg/day.⁴ The fludrocortisone dose can be adjusted to normalize renin plasma activity, and the required dose is typically slightly lower in patients on hydrocortisone as opposed to prednisone, as hydrocortisone has some mineralocorticoid activity itself.⁶ There is no easy way to assess



Figure 31.1 Hyperpigmentation in Addison disease.

the appropriateness of the glucocorticoid replacement dose as ACTH levels, although they do decline with appropriate treatment, generally do not normalize. Recurrent symptoms of adrenal insufficiency may suggest underreplacement, whereas development of Cushingoid features may suggest overreplacement. Patients are typically advised to increase their dose of glucocorticoids during stressful events such as illnesses or surgery. The hyperpigmentation seen in untreated Addison disease should resolve with appropriate treatment.

Patients with Addison disease are also dehydroepiandrosterone (DHEA) deficient, and some studies show symptomatic improvement in women who are given DHEA replacement as well.⁷ These findings, however, have not been consistently shown, and there is as, of yet, no consensus on whether DHEA replacement is appropriate.¹

During times of illness or in preparation for surgery, patients with Addison disease require extra doses of

glucocorticoids. The replacement dose varies based on the severity of the illness and the type of surgery. In minor illnesses, oral doses can be increased two- to threefold over the course of 3 days. Prior to a minor surgical procedure, a low dose of hydrocortisone is recommended the day of the procedure. For major surgical procedures, higher doses are required. In times of critical illness or stress, dose steroids are recommended.

CUSHING SYNDROME

Cushing syndrome results from excessive glucocorticoid exposure, most commonly due to exogenous steroid administration. Endogenous Cushing syndrome can occur from an adrenal tumor secreting excess cortisol, or a pituitary tumor or ectopic source of excess adrenocorticotropin (ACTH), leading to an increase in glucocorticoid production.

Whether endogenous or exogenous, glucocorticoid excess has several cutaneous manifestations. Excess glucocorticoids lead to fat deposits in the cheeks and dorsocervical area giving the characteristic “moon facies” and “buffalo hump.” Fat deposition in the abdomen leads to centripetal obesity. Less commonly, retroorbital fat deposits may cause exophthalmos. Muscle atrophy and wasting of the extremities also occur from excess glucocorticoid exposure.

Decreased collagen synthesis and epidermal cell division lead to many of the cutaneous findings, such as thin skin, easy bruising, and the classic abdominal striae of Cushing syndrome (Figure 31.2). The striae should be violaceous in color and greater than 1 cm in diameter to be pathognomonic for Cushing syndrome. Classically, they are found on the abdomen but can also occur on the aspect of the buttocks, breasts, and arms. These striae should be differentiated from those seen in obese or pregnant patients, which tend to be more pink and silvery, less violaceous, and thinner than 1 cm.

Hyperpigmentation in Cushing syndrome is uncommon but can be seen in cases of ectopic Cushing syndrome. The hyperpigmentation is mediated by excessive ACTH secreted by an underlying malignancy, which activates melanocyte-stimulating receptors. This hyperpigmentation may be generalized but mostly evident on sun-exposed areas (face, neck) and areas of mild pressure or friction (elbows, knuckles, knees). It may occur in pituitary Cushing syndrome, but usually

Addison Disease

Dermatologic features:

- Hyperpigmentation in sun-exposed areas
- Increased pigmentation of palmar creases, buccal mucosa
- Vitiligo or alopecia areata

Diagnosis:

- Cortisol <18 mcg/dL 60 minutes after 250 mcg ACTH stimulation test

Treatment:

Glucocorticoid replacement:

- Prednisone 5–7.5 mg daily
- or
- Hydrocortisone 15–20 mg morning and 5–10 mg afternoon

Mineralocorticoid replacement:

- Fludrocortisone 0.05–0.2 mg/day

Adrenal crisis: Stress doses steroids

- Hydrocortisone 100 mg IV q 6 hours

Source: Adapted from Grinspoon SK, Biller BM. Laboratory assessment of adrenal insufficiency. *J Clin Endocrinol Metab* 1994;79:923–931.



Figure 31.2 Abdominal striae of Cushing syndrome.

the levels of ACTH are not high enough as in ectopic cases. Hyperpigmentation would not be seen in adrenal Cushing syndrome, since the elevated cortisol feeds back to suppress ACTH production.

Diagnosis

The diagnosis of Cushing syndrome can be challenging. Elevated levels of random cortisol vary throughout the day and cannot be used to establish the diagnosis.

A 24-hour urinary free cortisol (UFC) has the highest sensitivity and specificity (95%–100%) to confirm the diagnosis.¹⁰ An adequate urine collection, in which the UFC is elevated at least three times the upper limit of normal, is diagnostic of Cushing syndrome. A normal 24-hour UFC excludes the diagnosis. A more widely used screening test, the low-dose dexamethasone suppression test, can also be performed, but it lacks specificity. At 11 PM, 1 mg of dexamethasone is administered, and a serum cortisol level is drawn the next morning at 8 AM. If the serum cortisol is less than 1.8 mcg/dL the diagnosis of Cushing syndrome can be excluded. False-positive results can occur in patients with depressive illness, obesity, chronic alcoholism, or those on antiseizure medications or estrogens. An abnormal result from the dexamethasone suppression test must be confirmed with a more specific test, such as the 24-hour UFC or late night salivary cortisol. Measuring late night salivary cortisol has a sensitivity and specificity of 95%–100%. Patients take samples of their saliva between 11 PM and midnight on three separate occasions. Cushing syndrome is confirmed by positive results on two separate occasions, using a combination of tests listed in Table 31.1.

Once, the presence of excess glucocorticoid production is confirmed, the source must be located. ACTH levels can differentiate an adrenal source (low ACTH) from a pituitary source (normal or high ACTH) or an ectopic source (very high ACTH). Imaging can then be directed to locate the tumor source. Differentiating between pituitary or ectopic ACTH production can be challenging and requires further testing with a high-dose dexamethasone suppression test or inferior petrosal sinus sampling.

Treatment

The treatment of Cushing syndrome is based on the etiology of excess glucocorticoid production. If it is caused by an ACTH-dependent pituitary tumor, transsphenoidal resection is the treatment of choice. An adrenalectomy is indicated, if an adrenal tumor is the cause of excess cortisol production. An ectopic source of ACTH secretion requires treatment of the underlying malignancy. Medications that decrease cortisol synthesis, such as ketoconazole and metyrapone, are available,

but they are reserved mainly for nonsurgical candidates or those with ectopic disease.

Cushing Syndrome

Dermatologic features:

- Abdominal striae, violaceous and >1 cm
- Skin atrophy
- Easy bruising
- Supraclavicular fat pads
- Moon facies

Diagnosis:

- 24-hour urinary free cortisol >3× upper limit of normal
- Late-night salivary cortisol > reference range (varies by assay)
- Imaging to locate tumor (adrenal versus pituitary versus ectopic)

Treatment:

- Surgical resection of the tumor source

Source: Adapted from Kronenberg HA et al. *Williams Textbook of Endocrinology*. 12th ed. June 2011; and Neiman LK et al. *J Clin Endocrinol Metab* 2008;93:1526–1540.

NECROLYTIC MIGRATORY ERYTHEMA IN GLUCAGONOMA

Glucagonoma is a pancreatic tumor arising from the α cells of the pancreatic islets and causing increased secretion of the pancreatic hormone glucagon. The clinical syndrome classically associated with glucagonoma includes necrolytic migratory erythema (NME), cheilitis, diabetes mellitus, anemia, weight loss, venous thrombosis, and neuropsychiatric findings. Weight loss and NME are the most prevalent manifestations, occurring in approximately 65%–70% of patients by the time of diagnosis. The dermatitis may occasionally appear, prior to the onset of systemic symptoms, but most patients with dermatitis usually have weight loss, diarrhea, sore mouth, weakness, mental status changes, or diabetes mellitus, as well as hypoaminoacidemia and zinc deficiency on laboratory analysis.⁸

Clinical Features

NME is considered the hallmark feature of the glucagonoma syndrome^{8,9} and is the clinical feature that leads to the diagnosis of glucagonoma syndrome in the majority of cases. NME is characterized by a painful and pruritic polymorphous eruption. It begins as an erythematous macular and papular skin eruption that later develops into well-demarcated plaques with variable scaling and finally progresses to centrally forming vesicles and bullae that rupture leaving a crusted and eroded surface^{8,9} (see Figure 31.3). NME has a relapsing remitting course. Individual lesions typically evolve over a period of time lasting 1–2 weeks, and patients will have multiple lesions in various stages of the cycle. These lesions are usually seen first in the groin, later progressing to the perineum, the buttocks, and the extremities (Figure 31.4).

NME is frequently complicated by secondary skin infections with *Candida albicans* or *Staphylococcus aureus* and, in fact,

Table 31.1 Tests for Cushing Syndrome

24 hour urinary free cortisol (two measurements)
Late-night salivary cortisol (two measurements)
Low-dose (1 mg) dexamethasone suppression test

Source: Shirodkar M. *Cutaneous Manifestations of Endocrine Disease. Textbook of Internal Medicine: An Intensive Board Review with 1000 MCQs*. Blendon-Miller 2015.



Figure 31.3 Necrolytic migratory erythema on the foot, showing indurated areas with blistering, crusting, and scaling.



Figure 31.4 NME.

some patients are diagnosed incorrectly with chronic candidosis years before eventually being diagnosed with NME.⁹

Diagnosis

The differential diagnosis for NME is large and includes acrodermatitis enteropathica (AE), pemphigus foliaceus, psoriasis, and chronic mucocutaneous candidosis,^{10,11} and should be differentiated on the basis of the larger clinical picture, histologic analysis, and laboratory findings. In patients in whom NME is suspected, one should check a glucagon level, and, if elevated, imaging should be done to look for a neuroendocrine tumor. Glucagon levels may be elevated in several conditions besides glucagonoma, including liver or kidney disease, prolonged starvation, or acute myocardial infarction, but a level greater than 1000 pg/mL is highly suggestive of glucagonoma.⁹ Given the often long delay in diagnosis from initial presentation of NME, some authors argue that glucagon levels should be checked in all patients with diabetes mellitus and a chronic cutaneous eruption.⁹

Skin biopsy specimens should be taken from the inner edge of an advancing lesion. The characteristic finding is necrosis of the upper layer of the stratum spinosum with separation from the underlying epidermis which is less affected.⁸

NME has occasionally been reported without evidence of glucagonoma. These patients typically have hyperglucagonemia or amino acid deficiency of another etiology. This is often called pseudoglucagonoma syndrome.¹²

Treatment

The treatment of choice for NME is complete surgical removal of the α -cell tumor and is the only chance for a cure of the disease. After surgical resection, there is normalization of glucagon levels. The eruption typically resolves rapidly, often within days, after removal of the tumor.¹³ Unfortunately, the majority of glucagonomas are either too large for curative surgery or already metastatic at the time of diagnosis. Due to the slow growth of these tumors, even in metastatic disease, debulking surgery may achieve a prolonged resolution of findings, although there is no evidence of prolonged survival.¹⁴ If full surgical resection is not possible due to the size of tumor or distant metastases, chemotherapy is added to decrease tumor bulk, and a long-acting somatostatin analog (a glucagon antagonist), such as octreotide, is used to relieve symptoms of NME.^{15,16} There have been case reports of successful surgical treatment of glucagonomas that are metastatic to the liver with liver transplant in addition to resection of the primary tumor. The role of liver transplantation in patients with metastatic glucagonoma is, however, not yet clear.¹⁷ Other treatments that have been tried with mixed results include intravenous amino acid and aggressive zinc supplementation.¹⁸

NME

Dermatologic features:

Erythematous plaques, painful and pruritic on extremities, cheilitis

Clinical features:

Weight loss, diarrhea, anemia, diabetes, deep vein thrombosis

Diagnosis:

Skin biopsy with necrosis of upper layers of stratum spinosum with separation from underlying epidermis

Serum glucagon levels >1000 pg/mL

Treatment:

Surgical resection of the pancreatic tumor

THYROID DYSFUNCTION

Thyroid disorders are common in the general population and can have varied dermatologic presentations based on the type and the severity of the thyroid dysfunction. Hyperthyroidism may be due to a transient thyroiditis, toxic nodules (either single or multiple), or, most commonly, Graves autoimmune thyroid disease. Hypothyroidism may be autoimmune Hashimoto, iodine-deficiency related, radiation induced, or postsurgical.

Clinical Features

Patients with hyperthyroidism have warm, moist, erythematous skin. Many patients develop onycholysis, and a significant

percentage of them complain of scalp hair loss. Alopecia areata and loss of body hair may also be noted, but are less common.

In addition, patients with Graves disease may show evidence of Graves ophthalmopathy, pretibial myxedema or acropachy. Pretibial myxedema can occur anywhere on the body but most commonly affects the anterior tibia and the dorsum of the feet. It is characterized by a nonpitting thickening and induration of the skin and is present in 0.5%–4% of patients with Graves disease.¹⁹ Acropachy is even less common, occurring in just 0.1%–1% of patients with Graves, and consists of a triad of digital clubbing, soft tissue swelling of hands and feet, and periosteal new bone formation.¹⁹ Both pretibial myxedema and acropachy are seen almost exclusively in patients with Graves ophthalmopathy, and these two dermatologic manifestations are considered indicators of more severe autoimmune disease.²⁰ Vitiligo, a marker of autoimmune disease, is also frequently seen in Graves disease.²¹

Patients with hypothyroidism, by contrast, have pale cold skin that is typically dry, rough, scaly, and hyperkeratotic.¹⁹ The skin may appear to have a yellowish discoloration, particularly in the palms, soles, and nasolabial folds, due to carotene deposition, and approximately 50% have a malar flush.^{4,19} Myxedema, caused by mucopolysaccharide deposition in the dermis, is most pronounced in the periorbital regions, leading to nonpitting swelling around the eyes. Loss of sympathetic tone may lead to a drooping of the upper eyelid. Patients may lose hair on the outer third of their eyebrows, and scalp hair loss has been reported in about half of all hypothyroid patients. Hair becomes dry and brittle, and nails are thin and grooved.¹⁹

Diagnosis

Serum TSH (thyroid-stimulating hormone) is the initial diagnostic test for either hyperthyroidism or hypothyroidism. In most cases of hyperthyroidism, the TSH will be suppressed, whereas in hypothyroidism the TSH will be elevated.²² Thyroid peroxidase antibody may be checked in hypothyroid patients to evaluate for Hashimoto (autoimmune) thyroiditis. After a laboratory diagnosis of hyperthyroidism is made, patients should be sent for a 24-hour radioactive iodine uptake and scan to determine the etiology, as an uptake and scan can differentiate between Graves, toxic nodules, and thyroiditis.

Treatment

Treatment of hypothyroidism is with levothyroxine weight-based dosing, typically 1.6 µg/kg/d, titrated to achieve a euthyroid state with TSH in the normal range.⁴ Any symptomatic patient with hyperthyroidism may be given a beta blocker, if there is no contraindication. Definitive treatment of hyperthyroidism varies depending on the etiology of the disorder. Thyroiditis typically resolves without treatment. In Graves disease or toxic nodules, radioactive iodine treatment is effective but frequently leads to hypothyroidism requiring levothyroxine therapy. In patients with Graves disease, antithyroid agents, such as methimazole and propylthiouracil, are other options; the remission rates after 18 months of medical treatment, however, are only 30%–40%, and these medications do come with the risk of allergic reactions or agranulocytosis.²³

FLUSHING AND CARCINOID SYNDROME

Carcinoids are slow-growing tumors arising from the enterochromaffin or Kulchitsky cells and in most cases originate in

Thyroid Diseases

Dermatologic manifestation in Graves disease:

Graves ophthalmopathy
Pretibial myxedema
Acropachy

Diagnosis:

Suppressed TSH, elevated free T3 and free T4, and
TSI (thyroid stimulating immunoglobulin)
Diagnosis confirmed by a thyroid uptake and scan

Treatment:

Radioactive iodine treatment
Antithyroid agents or surgery

Dermatologic manifestations of hypothyroidism:

Dry, scaly, hyperkeratotic skin
Periorbital myxedema
Brittle nails
Hair loss from scalp and eyebrows

Diagnosis:

Elevated TSH, low free T4

Treatment:

Levothyroxine

the gastrointestinal (GI) tract or the lungs. Carcinoid tumors can secrete any number of bioactive substances, and their presentation is dependent on both the type of substances secreted, as well as the location of the original tumor and any metastases. Carcinoid tumors typically produce large amounts of serotonin. In addition, they may also secrete histamine, corticotropin, dopamine, substance P, neurotensin, prostaglandins, kallikrein, and tachykinins.²⁴ Carcinoid syndrome is the term used to describe a constellation of signs and symptoms caused by the secreted bioactive substances and is present in less than 10% of patients with carcinoid tumors. The bioactive products produced by carcinoid tumors are inactivated in the liver, so patients with GI carcinoids develop carcinoid syndrome only if they have hepatic metastases, leading to secretion of the substances into the hepatic veins, whereas patients with carcinoid of the lung can develop carcinoid syndrome in the absence of metastatic disease.

Clinical Features

Episodic cutaneous flushing is the hallmark of carcinoid syndrome and is seen in 85% of patients.²⁵ The flushing of carcinoid is typically confined to the face, neck, and upper trunk. Carcinoid tumors originating in the midgut (appendix, ileum, jejunum) produce what is known as the classical carcinoid flush, which is a rapid-onset cyanotic flush lasting approximately 30 seconds and associated with a mild burning sensation. Foregut carcinoids (stomach, lung, pancreas, biliary tract) produce a brighter pinkish-red flush that may be pruritic and can be more difficult to differentiate from physiological flushing. Flushing episodes may occur spontaneously or may be provoked by certain triggers, similar to the triggers of physiologic flushing (alcohol, cheese, coffee, exercise, or emotional stressors).^{26,27} Carcinoid flushing often is associated with diarrhea and breathlessness or wheezing, and these associated signs are a method of differentiating the flushing of carcinoid from physiologic flushing.²⁸ Features of rosacea or vascular telangiectasias may develop after years of flushing. Severe flushing can also be associated with a drop in blood pressure and tachycardia. A phenomenon known as carcinoid crisis can be precipitated by anesthesia or

an interventional procedure and is characterized by a profound and prolonged hypotension with tachycardia.

Other clinical features of the carcinoid syndrome include niacin deficiency and hypoproteinemia from diversion of tryptophan for the synthesis of serotonin. Pellagra (glossitis, scaly skin, angular stomatitis, and confusion), as well as dependent edema, may develop secondary to these deficiencies but are usually a later presentation of the carcinoid syndrome.^{24,25,28} Scleroderma, without Raynaud phenomenon, also has been described in association with carcinoid syndrome and is considered a poor prognostic indicator.²⁸

Diagnosis

Signs of flushing, diarrhea, and bronchospasm, typically paroxysmal, may raise the suspicion for carcinoid syndrome. Additional less specific findings may include GI discomfort, a palpable abdominal mass, GI bleeding, or heart failure. The manifestations of carcinoid are protean, as they vary depending on the type of bioactive substances secreted and the location of the tumor. As such, patients are often initially misdiagnosed with other conditions, such as irritable bowel syndrome, asthma, or anxiety, and accurate diagnosis and treatment are delayed.

Although carcinoid may be suspected from the clinical presentation, the diagnosis must be confirmed with biochemical tests. The most specific test is a measurement of 24-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), a degradation product of serotonin. The test for urinary 5-HIAA has a sensitivity of 75% and a specificity of 88%,²⁴ but there are some drawbacks. Certain serotonin-rich foods, such as bananas, avocados, and tomatoes can increase urinary 5-HIAA and lead to false-positive results. Serum chromogranin A (CgA) is another biochemical test commonly used for the diagnosis of carcinoid. CgA is a constitutive secretory product of most neuroendocrine tumors, and plasma CgA levels have a sensitivity of up to 99% in diagnosing carcinoid. Plasma CgA is thus a sensitive, but not specific, marker for carcinoid tumors, as it may be elevated in several other neuroendocrine tumors as well as in cases of renal impairment, liver failure, and inflammatory bowel disease²⁴ or in patients on proton pump inhibitors.²⁹ A single recent study of the efficacy of plasma 5-HIAA in detecting carcinoid tumors demonstrated a sensitivity of 89% and a specificity of 97%,³⁰ but this test is not yet part of the standard armamentarium.

After carcinoid is confirmed by biochemical testing, localization of the primary tumor, as well as any metastasis, must be done; there are several different imaging modalities from which to choose. Octreotide scintigraphy, using In-111, is the initial modality of choice, if it is available. Octreotide scintigraphy has an overall sensitivity of 80%–90%, based on various studies.³¹ In addition to the high sensitivity, octreotide scintigraphy allows imaging of the entire body in one session, thereby detecting primary tumors as well as metastasis (which may be missed with conventional imaging). Bone scintigraphy is used to detect bone metastases, if they are suspected, and ¹²³I-MIBG scintigraphy also can be used to localize carcinoid, although it appears to be less sensitive than octreotide scintigraphy, especially in detecting metastases.³¹ Computed tomography and magnetic resonance imaging scans are frequently used for initial localization with a sensitivity for both of approximately 80%. Radiographic findings include mass lesions with calcification and stranding fibrosis. Other modalities frequently used for localization include positron emission

tomography scan (sometimes in combination with octreotide scintigraphy), endoscopic ultrasound, and endoscopy.

Treatment

Surgery is the only curative treatment for carcinoid tumors. Unfortunately, curative surgery is possible only with nonmetastatic disease or in resectable nodal or hepatic metastases, and most patients have significant metastatic disease at the time of presentation. Even in patients who have metastatic disease, surgery has a role for relief of mechanical obstructions and, in cases of carcinoid syndrome, debulking causes significant relief of signs and symptoms. Similarly, reduction of hepatic metastases, via surgical resection or hepatic artery occlusion (ligation, embolization, or chemoembolization), has been shown to give symptomatic relief from the carcinoid syndrome, and some studies have shown survival benefits of up to 2 years.³²

Medical treatment with somatostatin analogs (octreotide and lanreotide) has proven extremely efficacious for symptomatic relief, leading to resolution of flushing and diarrhea in 70%–80% of patients. In addition, urinary 5-HIAA levels were halved in 72% of patients.³³ Intravenous octreotide infusion has been used to successfully treat carcinoid crisis. The somatostatin analogs do not, however, appear to have any effect on tumor size or growth rate.^{24,26} Other medical treatments commonly employed in metastatic carcinoid include interferon- α and chemotherapy agents. Lifestyle modifications to avoid the triggers of flushing episodes, such as alcohol, exercise, and spicy food, are also encouraged, and diet supplementation with nicotinamide may prevent the symptoms of niacin deficiency.

Carcinoid Syndrome

Dermatologic manifestations:

Episodic violaceous flushing of face, neck, and chest
Venous telangiectasia of nose and upper lip

Clinical symptoms:

Secretory diarrhea, wheezing, right-sided valvular disease

Diagnosis:

24 hour urine 5-HIAA
Octreotide scintigraphy for tumor localization

Treatment:

Surgical resection of the tumor

URTICARIA PIGMENTOSA AND MASTOCYTOSIS

Mastocytosis is a group of rare disorders affecting adults and children and is distinguished by a pathologic increase in mast cells.²⁵ This increase in mast cells may be seen in a variety of tissues including the skin, bone marrow, GI tract, spleen, liver, and lymph nodes. The symptoms of mastocytosis are heterogeneous²⁵ and tend to be related to the level of mast cell burden and the tissue type involved. Symptoms are typically related to mast cell mediator release. The mediators found within mast cells are legion, including histamine, prostaglandin D₂, leukotrienes, interleukin-6, and many more. Patients with mastocytosis tend to experience symptoms in discrete attacks, when mast cell mediators are released. Manifestations typically include pruritus, whealing, flushing, palpitations, and tachycardia. Bone marrow involvement, common in adult cases of mastocytosis, can lead to anemia and low bone density. If there is

GI involvement, patients may experience diarrhea and abdominal pain. Strong stimuli of mast cell release can lead to anaphylactoid reactions with severe, prolonged hypotension. Mastocytosis can also present as idiopathic anaphylaxis in previously undiagnosed patients.

Clinical Features

The characteristic feature of mastocytosis is a dermatitis known as urticaria pigmentosa (UP). UP is the presenting feature in the majority of patients with systemic mastocytosis but can also be present as a cutaneous mastocytosis, without any extracutaneous involvement. The classic lesion³⁴ is a hyperpigmented reddish-brown macule or papule (see Figure 31.5). Another feature seen in UP is the local whealing and development of edema around the lesions when rubbed or scratched, known as Darier's sign. In typical UP in adults, the lesions measure 3–4 mm individually and are symmetrically and randomly distributed, with the highest density of lesions seen on the trunk and thighs and with relative sparing of the palms, soles, and face. In extensive cutaneous disease, the lesions may become confluent. Children tend to present with larger lesions (5–15 mm), and their lesions are most prominent on the trunk.³⁴

Pruritus is typically associated with UP. Less common presentations of UP include telangiectatic, nonpigmented, nodular, or plaque-like variations of the dermatitis.³⁴ In rare cases, mastocytosis can present as a single large mastocytoma instead of the diffuse eruption.

Diagnosis

The diagnosis of UP is based on clinical suspicion from the maculopapular lesions and Darier's sign and is confirmed by histopathologic examination of a tissue specimen. Skin biopsy of a UP lesion typically shows aggregates of mast cells within the papillary dermis and extending into the reticular dermis,³⁵ particularly around blood vessels. Mast cells within skin biopsies show a characteristic spindle shape with metachromatic granules. Another characteristic of UP on skin biopsy is the absence of any inflammatory cells other than mast cells in the dermal infiltrate.³⁶ The most specific stain for mast cells in any

Table 31.2 Diagnostic Criteria for Systemic Mastocytosis

Major criteria

Multifocal infiltrates of mast cells in bone marrow biopsy or in other extracutaneous organs

Minor criteria

>25% of mast cells in bone marrow biopsy or tissue specimens are spindle shaped or atypical

Detection of a codon 816 c-kit point mutation in blood, bone marrow, or lesional tissue

Mast cells in blood, bone marrow, or lesional tissue expressing CD25 or CD2

Baseline total tryptase level >20 ng/mL

tissue is immunohistochemical staining with tryptase.³⁷ The diagnosis of mastocytosis is occasionally made in patients lacking the typical dermatitis, by bone marrow biopsy, typically done after unexplained anaphylaxis or flushing or for peripheral blood abnormalities.

When the diagnosis of UP is made, it is important to determine whether the patient has cutaneous mastocytosis alone or whether there is systemic involvement. A set of major and minor diagnostic criteria exist to diagnose systemic mastocytosis (see Table 31.2). A diagnosis of systemic mastocytosis requires the fulfillment of either one major criterion with one minor criterion or three minor criteria.^{38,39} More extensive cutaneous disease tends to correlate with increased risk for systemic mastocytosis. Elevated levels of mast cell mediators, such as tryptase and histamine, also can be used to support the diagnosis of systemic mastocytosis. Serum tryptase levels greater than 20 ng/mL are suggestive of systemic mastocytosis, whereas patients with only cutaneous mastocytosis tend to have levels less than 14 ng/mL.⁴⁰ Histamine metabolites in a 24 hour urine collection also tend to be increased in systemic mastocytosis.⁴¹ This test, however, is neither more sensitive nor more specific than the serum tryptase level.⁴² Bone marrow involvement is seen in the vast majority of patients with adult-onset mastocytosis. As a result, a bone marrow biopsy is recommended in the evaluation of all patients with adult-onset disease, whereas in children with cutaneous disease, bone marrow biopsy is recommended only in the presence of other abnormal findings suggesting systemic involvement, such as an abnormal complete blood count or an enlarged spleen or liver.

Treatment

Most patients, be they children or adults, have an indolent course and a good prognosis; however, there is no definitive treatment for mastocytosis. Treatment instead is directed toward the amelioration of clinical manifestations, related to the release of mast cell mediators and must be tailored to each patient's specific findings and organ involvement. All patients may be counseled in the avoidance of triggers, such as exercise, rapid temperature changes, skin rubbing, or certain drugs including anesthesia medications. Histamine receptor blockers (H1 and H2), along with cromolyn, are effective for pruritus and for episodes of flushing, diarrhea, or abdominal pain.³⁵ Topical glucocorticoids can be used for symptomatic skin lesions. Ultraviolet light PUVA (psoralen plus ultraviolet A) is used in the treatment of UP to decrease pruritus, whealing, and flare reactions.⁴³ Bone disease from marrow involvement can be treated similar to osteoporosis of other etiologies, with calcium, vitamin D, and bisphosphonates. Patients with anaphylactic



Figure 31.5 Urticaria pigmentosa on the back with hyperpigmented reddish-brown macules and papules.

reactions are treated with epinephrine and should be given an epinephrine emergency pen to carry with them. For patients with more aggressive systemic disease, other treatments (such as chemotherapy, interferon- α , and splenectomy) have been tried with mixed results.

Mastocytosis

Dermatologic finding:

Urticaria pigmentosa and Darier's sign

Systemic findings:

Pruritus, flushing, palpitations, tachycardia

Diagnosis:

Skin biopsy consistent with aggregates of mast cells in the dermis

(Systemic mastocytosis: elevated serum tryptase and 24-hour urine histamine)

Treatment:

Histamine receptor blockers, topical glucocorticoids, ultraviolet light PUVA



Figure 31.7 Necrobiosis lipoidica.

DIABETES MELLITUS

Diabetes mellitus is a group of disorders characterized by hyperglycemia due either to a deficiency of insulin secretion (type 1 diabetes), a resistance to insulin, or both (type 2 diabetes). Classic symptoms of diabetes include polyuria, polydipsia, and weight loss, but diabetes can be associated with several skin disorders both infectious and noninfectious in etiology.

Clinical Features

Common noninfectious skin findings in diabetics include acanthosis nigricans (AN; Figure 31.6), skin tags, vitiligo, necrobiosis lipoidica (Figure 31.7), and diabetic dermopathy. AN presents as hypertrophic, hyperpigmented velvety plaques seen in the body folds, most commonly in the axillae and nape. AN is generally asymptomatic and is more common in patients with type 2 diabetes, but it can be seen in other diseases that cause insulin resistance, such as acromegaly and Cushing disease. Skin tags, or acrochordons, are another skin



Figure 31.6 Acanthosis nigricans.

manifestation of insulin resistance, and 66%–75% of patients with skin tags have diabetes.⁴⁴ Skin tags are found most frequently on the eyelids, neck, and axillae. Vitiligo is an autoimmune disorder and, due to similar etiologies, is seen more frequently in type 1 (autoimmune) diabetes. Necrobiosis lipoidica (NL) is a rare but specific skin manifestation of diabetes. It occurs in only 0.3% of all diabetic patients, most of whom are insulin dependent at the time of presentation, and is more common in men.⁴ NL consists of distinctive oval or irregularly shaped plaques with red or violaceous borders, central atrophy, and yellow pigmentation, typically occurring on the anterior aspect of the shins. Up to 35% of these lesions result in ulceration.⁴ Diabetic dermopathy, or shin spots, is seen in 40% of diabetic patients and is more common in men and in patients with evidence of other end-organ damage, such as retinopathy, neuropathy, or nephropathy. The lesions of diabetic dermopathy begin as groups of red macules on the shins that over time become shallow or depressed and hyperpigmented.

Skin infections are also common in diabetics, occurring in 20%–50% of all diabetic patients, more commonly in patients with type 2 diabetes and in patients with poor glycemic control, and can vary in severity from a simple superficial cellulitis to necrotizing fasciitis.⁴⁴ Patients with poor diabetic control have both higher rates of colonization and higher rates of skin infection with *C. albicans*, *Staphylococcus* species, and *Streptococcus* species. Women with hyperglycemia and glycosuria frequently complain of recurrent vaginal yeast infections. Elderly diabetics can develop malignant external otitis, an invasive infection of the external auditory canal that typically occurs in immunocompromised patients, and *Pseudomonas aeruginosa* is the causative organism in more than 95% of cases.⁴⁵

Diagnosis

The diagnosis of diabetes can be made in one of three ways. The preferred method is the use of a fasting plasma glucose of 126 mg/dL (7.0 mmol/L) after a fast of at least 8 hours or a hemoglobin A1c > 6.5 g/dL. Other acceptable

criteria for diagnosing diabetes include findings of hyperglycemia (polyuria, polydipsia, weight loss) along with a random plasma glucose greater than or equal to 200 mg/dL (11.1 mmol/L) or an oral glucose tolerance test using a 75 g glucose load with a 2 hour plasma glucose level greater than or equal to 200 mg/dL.⁴⁶

On histopathologic examination, acanthosis nigricans lesions appear hyperkeratotic with papillomatosis. The dark color of the lesions is due to the thickness of the superficial epithelium, but there is no change in melanocyte number or melanin content.⁴⁷ The lesions of diabetic dermopathy show basement membrane thickening, whereas NL is characterized by a degeneration of collagen with granulomatous inflammation of the subcutaneous tissues and blood vessels.^{48,49} The yellow central area of the necrobiotic lesions is due to the thinning of the dermis, making subcutaneous fat more visible.⁵⁰

Treatment

The treatment of diabetes focuses on normalization of blood glucose levels, as well as aggressive management of known complications of diabetes, such as cardiovascular disease. Type 2 diabetes can be treated with oral medications (e.g., secretagogues, biguanides, thiazolidinediones dipeptidyl peptidase-4 inhibitors, sodium glucose cotransporter-2 inhibitors), with injectable drugs (e.g., glucagon-like peptide-1 agonists, insulin, pramlintide), or with a combination of both. Type 1 diabetes, however, must be treated with insulin; sometimes pramlintide is added. Improved glycemic control decreases the incidence of skin infections and delays progression to microvascular disease complications, such as retinopathy and nephropathy.

Most of the noninfectious skin manifestations of diabetes are asymptomatic and do not require treatment. Acanthosis nigricans, diabetic dermopathy, and skin tags are generally asymptomatic and require no treatment. If desired, however, skin tags can be removed by snipping, cryosurgery, lasersurgery, or electrodesiccation, and acanthosis may be ameliorated by weight loss. Necrobiosis lipoidica has no standardized treatment; however, most treatments employ corticosteroids, topically or intralesionally.⁵⁰

Diabetes

Dermatologic manifestations:

Acanthosis nigricans, necrobiosis lipoidica, diabetic dermopathy

Diagnosis:

Fasting glucose >126 mg/dL, HgA1c >6.5, random glucose <200 mg/dL

Treatment:

Glycemic control, which may or may not lead to improvement in dermatologic manifestations

PORPHYRIA CUTANEA TARDA

Porphyria cutanea tarda (PCT) is the most common of the porphyrias and is caused by a disruption of heme biosynthesis due to decreased activity of the enzyme uroporphyrinogen decarboxylase (UROD), the fifth enzyme in the heme biosynthetic pathway. PCT may be sporadic or inherited. Sporadic PCT makes up 80% of cases and is caused by an acquired deficiency of UROD (uroporphyrinogen decarboxylase) activity in

the liver.⁵¹ Twenty percent of cases are inherited as an autosomal dominant trait with low penetrance.⁵¹ There are reports of PCT developing after exposure to certain chemical such as fungicides, herbicides, and polyhalogenated hydrocarbons.⁵²⁻⁵⁴ Most cases of PCT are associated with some sort of precipitant. Precipitants include alcohol, estrogens, viral infections, and iron overload, in individuals who are susceptible to the disease.⁵⁵ In addition, an association has been found between PCT and the hemochromatosis gene mutations C28Y.⁵⁶

Clinical Features

PCT is characterized by photosensitive cutaneous lesions with increased skin fragility manifesting as vesicles, bullae, blisters, and sores (see Figure 31.8). The bullae rupture easily, crust over, and frequently become secondarily infected. Lesions are seen most commonly on the hands and forearms but can be found on any sun-exposed area and may heal with areas of hypopigmentation or hyperpigmentation or sclerodermatous changes.⁵⁷ Milia are frequently seen on the hands and fingers. Increased facial hair is common and is more noticeable in women.

Diagnosis

The characteristic finding of PCT on histopathologic examination is subepidermal bullae with minimal inflammation. The dermal papillae have an undulating base and are referred to as "festooned."⁵⁷ Liver biopsy findings include red autofluorescence under a Wood lamp as well as mild steatosis, siderosis, and focal lobular necrosis with pigment-laden macrophages. Birefringent needle-like cytoplasmic inclusions may be present in hepatocytes and are specific for PCT.⁵⁸ Serum iron and hepatic transaminase levels are elevated in most patients with PCT. Urine studies will show a marked increase in urinary uroporphyrins. An analysis of urinary porphyrins showing greater amounts of uroporphyrin versus coproporphyrin is consistent with PCT.⁵⁹

Treatment

General measures in the management of PCT include avoidance of precipitating factors such as alcohol, estrogens, iron,



Figure 31.8 Porphyria cutanea tarda with hand lesions presenting as vesicles, bullae, blisters, and sores.

and strong sunlight. If these measures are not sufficient, then phlebotomy is the treatment of choice for PCT. The goal of phlebotomy is to deplete body iron stores and produce a mild iron deficiency. Clinical improvement is typically seen starting 2–3 months after initiation of phlebotomy. If phlebotomy is contraindicated or unsuccessful, then chloroquine is an alternative treatment.⁶⁰

Porphyria Cutanea Tarda (PCT)

Dermatologic manifestations:

Photosensitive cutaneous lesions, with vesicles and bullae

Diagnosis:

Subepidermal bullae with minimal inflammation
Elevated hepatic transaminases and iron levels
Elevated urinary uroporphyrins

Treatment:

Phlebotomy
Chloroquine
Avoidance of triggers

CONGENITAL ICHTHYOSIS AND TYPE II GAUCHER DISEASE

Gaucher disease is the inherited autosomal recessive deficiency of lysosomal glucocerebrosidase. There is significant clinical heterogeneity within Gaucher disease related to the severity of the mutations affecting the glucocerebrosidase.⁶¹ The disease is divided into three different types based on phenotypic presentation. Type I is known as nonneuronopathic Gaucher disease. It is by far the most common type, and patients may remain asymptomatic or may present with cytopenia, hepatosplenomegaly, or bone involvement. Type II, acute neuronopathic Gaucher disease, is uniformly fatal with death typically occurring by early childhood; it is within this type that one can see presentations of congenital ichthyosis, or collodion baby syndrome. Type III, chronic neuronopathic Gaucher disease, presents with variable degrees of systemic involvement plus one or more neurologic manifestations.

Clinical Features

Type II Gaucher disease is the rarest and most severe form of the disease, and it is within this type that one can see presentations of congenital ichthyosis, or collodion baby syndrome. Congenital ichthyosis presents in neonates with red, dry, tight, hyperkeratotic, scaling skin throughout the body, often associated with joint abnormalities and contractures as well as other systemic signs of Gaucher, such as hepatosplenomegaly and neurologic changes.⁶² There have been case reports of patients presenting with congenital ichthyosis prior to neurologic deterioration that develops in subsequent months.⁶³

Diagnosis

The skin changes in type II Gaucher disease are related to the loss of glucocerebrosidase, leading to an increased ratio of glucosylceramide to ceramide in the lipid makeup of epidermal cells.⁶⁴ Ceramides are major components of the lipid bilayer in the normal epidermis, necessary for permeability barrier

homeostasis. A paucity of ceramides leads to an inability to form a competent epidermal barrier, and as a result, the lipid bilayer has a serrated, abnormal appearance.^{64,65} Epidermal hyperplasia and hyperproliferation are also seen and have been hypothesized to be due to stimulation of cellular proliferation by the accumulated glucosylceramide.⁶⁶

Histologic examination of skin from patients with congenital ichthyosis shows dense hyperkeratosis, epidermal hyperplasia, and inflammation. Ultrastructural examination reveals disruptions in the normal lamellar bilayer in the stratum corneum, as well as a reversal of the normal ratio of sphingolipids in the stratum corneum, with much higher levels of glucosylceramide to ceramide in the type II Gaucher patients.^{62,64} Significantly, these ultrastructural skin changes can be seen in all patients with type II Gaucher disease, whether or not they show skin changes clinically. In addition, these changes are seen only in type II Gaucher disease and are not present in type I or type III. These skin findings, thus, represent a method for early discrimination of type II from the other, milder types of Gaucher disease. Early differentiation of type II disease can aid in appropriate management and counseling, as neither enzyme activity nor genotypic analysis is able to determine the specific type of Gaucher disease.⁶⁴

Treatment

There is, unfortunately, no treatment to halt or reverse the effects of type II Gaucher disease. Placental human glucocerebrosidase and recombinant glucocerebrosidase have been used as enzyme replacement therapy in type I and type III disease and have been effective in treating the visceral and hematologic manifestations, but these treatments have shown disappointing results in type II disease and do not appear to alter the course of neurologic deterioration.⁶²

Type II Gaucher Disease

Dermatologic manifestations:

Congenital ichthyosis, hyperkeratotic, scaling skin

Diagnosis:

Decreased glucocerebrosidase activity, mutation analysis

Treatment:

Supportive

FABRY DISEASE

Fabry disease is a rare, X-linked lysosomal storage disease.⁶⁷ Patients with Fabry disease are deficient in the enzyme α -galactosidase A (α -gal A), which leads to the buildup of neutral glycosphingolipids in a range of tissues within the body. The clinical manifestations of Fabry disease are seen primarily in affected hemizygous men and to some extent in heterozygous women. The disease is slowly progressive; affected men have a shortened life expectancy of approximately 50 years, and heterozygous women have a life expectancy of 70 years with the main causes of death being renal failure, heart disease, or stroke.

Clinical Features

The characteristic dermatologic manifestation of Fabry disease is angiokeratoma. These lesions can occur at any time but typically

first appear between 5 and 13 years of age.^{67,68} The initial lesion is dark red, telangiectatic, and up to 4 mm across and does not blanch with pressure. Overlying hyperkeratosis may or may not be present. Lesions typically occur in symmetrical clusters and are seen most commonly in the areas between the umbilicus and the knees. In men, the first lesions are frequently seen on the scrotum. The number of lesions increases with age in the majority of patients, and the extent of cutaneous involvement correlates with the severity of the systemic manifestations of the disease.⁶⁹

Other cutaneous findings in Fabry disease include telangiectasias, disorders of sweating, decreased body hair, and edema. Telangiectasias are characteristic of Fabry disease but are not specific, as they can be seen in several other conditions. The most commonly reported sweating disorders are hypohidrosis or anhidrosis, associated with heat and exercise intolerance; hyperhidrosis has been reported, as well.

In addition to cutaneous manifestations, several systemic effects are frequently seen, including such multiple cardiac and cardiovascular manifestations as hypertension, cardiomegaly and stroke, renal failure, neuropathic pain, cataracts, and corneal dystrophy.

Diagnosis

In men, the diagnosis can be made based on the presence of cutaneous angiokeratomas in the setting of a positive family history, specifically of early deaths due to kidney or heart disease. Under light microscopy, angiokeratoma lesions are composed of a thin epidermis, below which the upper portion of the dermis is filled with dilated blood-filled vessels.⁷⁰ A hyperkeratotic stratum corneum may or may not be present. Further testing will reveal a deficiency of α -gal A in several tissues, including serum, tears, and tissue specimens. Lipid inclusions with birefringent "Maltese crosses," as well as fat-laden epithelial cells, may be seen in the urine.

In female heterozygotes, the findings are seen only in a minority of affected patients and tend to be milder. The variability of presentations in female heterozygotes is believed to be due to variations in selective X-chromosome inactivation. Affected women may have α -gal A levels within the normal range, so genetic analysis is recommended.⁶⁷

Treatment

Treatment of Fabry disease has been focused mainly on symptomatic relief up to this point; there is now, however, growing evidence of the effectiveness of enzyme replacement therapy. The mainstay of treatment for angiokeratomas has been the application of various types of laser surgery. Recent trials of enzyme replacement therapy with two different preparations of bioengineered enzyme have shown beneficial effects on signs and symptoms, such as pain, renal and cardiac

complications, and overall quality of life.⁷¹ In addition, enzyme replacement therapy has been shown to clear the deposits of neutral glycosphingolipids from the kidneys, hearts, and skin of patients with Fabry disease.⁷²

ZINC DEFICIENCY

Zinc is an essential mineral for humans. It is present in more than 100 metalloenzymes, such as alkaline phosphatase and carbonic anhydrase, and appears to play an important role in protein and carbohydrate metabolism as well as cell proliferation, healing and tissue repair, and growth and development. Zinc is absorbed from the proximal portion of the small intestine and is excreted through intestinal and pancreatic secretions. It is also present in human breast milk.

Zinc deficiency can be either acquired or inherited. The inherited congenital form is known as acrodermatitis enteropathica (AE) and is a rare autosomal recessive partial defect in zinc absorption, occurring in approximately 1 in 500,000 children.⁷³ In AE, patients present in infancy within days, if the infant is bottle fed and at the time of weaning, if breast fed. Most acquired forms of zinc deficiency, however, do not present until later in development. Acquired zinc deficiency can be caused by inadequate dietary intake of zinc or from malabsorption of zinc, usually due to diseases, such as celiac sprue, Crohn disease, cystic fibrosis, or short gut syndrome. Dietary zinc deficiency is common in certain parts of Southeast Asia and sub-Saharan Africa, but it is rare in the developed world. There are certain subpopulations, however, that are at increased risk; these include vegetarians, alcoholics, premature infants, and malnourished persons.⁷⁴

Clinical Features

The dermatitis seen in zinc deficiency is similar in both the acquired and inherited forms and is also largely indistinguishable from the dermatitis seen in glucagonoma, vitamin B₃ (niacin) deficiency, and in other vitamin deficiencies. The dermatitis is characterized by eczematous, erythematous scaly plaques over the acral and periorificial areas. These plaques may become vesicular, bullous, or desquamative. The skin can become secondarily infected, typically with *C. albicans*. Other commonly seen features include angular cheilitis, stomatitis, and nail changes, such as onychodystrophy, onycholysis, and paronychia.⁷⁵ If left untreated, these patients will go on to develop generalized alopecia, as well as diarrhea.⁷⁶ Other possible findings are photophobia, irritability, loss of appetite, poor wound healing, growth retardation, and hypogonadism.

Diagnosis

Histopathologic examination of skin biopsy specimens is non-specific and indistinguishable from other vitamin deficiency dermatoses and glucagonoma. The most common findings are parakeratosis and necrolysis, cytoplasmic pallor, vacuolization, and ballooning degeneration also seen in the NME of glucagonoma.⁷³ Diagnosis should be based on clinical suspicion and confirmed by laboratory testing. Plasma zinc level is the most commonly used test, although because only 0.1% of the body's total zinc stores is manifested in plasma zinc, it is an imperfect measure of total body zinc. A fasting morning plasma zinc level less than 50 μ g/dL is suggestive of zinc deficiency. Other

Fabry Disease

Dermatologic manifestations:

Angiokeratoma, telangiectasias

Diagnosis:

Mutation analysis α -Gal A gene

Low serum α -Gal A activity

Treatment:

Enzyme replacement therapy (ERT)

laboratory tests to support the diagnosis include a low level of serum alkaline phosphatase, a zinc-dependent metalloenzyme, and a low level of urinary zinc excretion.⁷⁷⁻⁷⁹

Treatment

Treatment of zinc deficiency involves zinc supplementation. It is important to distinguish acquired zinc deficiencies from AE, because acquired deficiencies require only limited treatment durations, whereas inherited AE requires life-long treatment. In AE, the recommended initial dosing starts at 3–10 mg/kg/d and maintenance dosing of 1–2 mg/kg/d, whereas the recommended dose for dietary deficiency is lower, at approximately 0.5–1 mg/kg/d.^{73,80} Zinc can be administered in many preparations, but zinc sulfate appears to be the best tolerated.⁷⁵ Clinical improvement is typically seen within days to weeks of initiating zinc replacement therapy,⁸¹ often long before a change in the plasma zinc levels can be seen. The most common side effect of zinc supplementation is GI irritation with resultant symptoms of nausea, vomiting, and gastric hemorrhage. Zinc has also been implicated in impaired copper absorption, so copper serum levels must be monitored, as well, in these patients.

Zinc Deficiency

Dermatologic manifestations:

Eczematous, erythematous scaly plaques of anogenital and oral areas

Diagnosis:

Low plasma zinc levels

Treatment:

Zinc supplementation

VITAMIN DEFICIENCY

Vitamin A

Vitamin A is a fat-soluble vitamin found in meats, dairy products, and certain vegetables (e.g., carrots, spinach, kale, peas, cantaloupe). Due to the abundance of vitamin A in the food supply, deficiency of vitamin A is quite rare in Western countries but is common in developing countries, where malnutrition is prevalent. It also can be seen in patients with anorexia nervosa; in those with fat malabsorption syndromes, such as Crohn disease, celiac disease, pancreatic insufficiency, biliary disease, and cystic fibrosis; and in persons who have had GI surgery.⁸²⁻⁸⁴

Clinical Features

Deficiency of vitamin A typically presents with ocular findings, such as conjunctival xerosis, white patches on the sclera (known as Bitot spots), and night blindness, but it also can present with cognitive disturbances or growth failure.⁸² Cutaneous manifestations of vitamin A deficiency may overlap with features of other nutritional deficiencies. The most common finding is phrynoderma, a form of follicular hyperkeratosis characterized by hyperkeratotic papules on the extensor surfaces of the extremities, shoulders, and buttocks. These papules tend to coalesce to form plaques, and in severe phrynoderma,

they can cover the entire body.⁸³ Phrynoderma was previously thought to result exclusively from vitamin A deficiency, but studies in recent years have associated the disease with deficiencies in the B vitamins, vitamin E, essential fatty acids, and general malnutrition.⁸³⁻⁸⁶

Diagnosis and Treatment

Diagnosis of vitamin A deficiency is made by identification of typical ocular findings and confirmed by laboratory testing of serum vitamin A levels. Manifestations of deficiency typically resolve with vitamin A replacement. Phrynoderma traditionally has been treated with cod liver oil (which contains vitamin A),⁸³ and more recently treatment with safflower oil, vitamin B complex, and vitamin E have been associated with diminution of phrynoderma and visual findings.⁸⁶

Vitamin A Deficiency

Dermatologic manifestations:

Phrynoderma: follicular hyperkeratosis

Diagnosis:

Low serum vitamin A levels

Treatment:

Vitamin A replacement

Riboflavin (Vitamin B₂)

Riboflavin deficiency is rare in developed countries, due to the abundance of this water-soluble vitamin in the food supply. Riboflavin is found in meats, fish, green leafy vegetables, dairy products, and fortified cereals. Riboflavin deficiency is typically seen with malnutrition, and in Western countries, it can be found in liver disease and in infants treated with phototherapy for neonatal jaundice.^{82,84}

Clinical Features

Typical cutaneous features of riboflavin deficiency involve the mucous membranes and frequently overlap with signs and symptoms of other vitamin deficiencies. Cutaneous manifestations of chronic deficiency include scaling of the lips, angular stomatitis, glossitis, monilial intertrigo, and scrotal dermatitis.^{82,84,87}

Diagnosis and Treatment

Diagnosis can be made with plasma riboflavin concentration or erythrocyte glutathione reductase activity.^{82,84} As other nutritional deficiencies may coexist, however, the diagnosis of riboflavin deficiency is commonly made based on clinical suspicion and confirmed by rapid improvement in symptoms and signs after repletion of riboflavin stores. Replacement of riboflavin is given as 1 mg/d in infants and 3 mg/d in children.⁸²

Niacin (Vitamin B₃)

Similar to riboflavin, niacin is found in meats, dairy products, fortified cereals, and legumes and is synthesized in the body from dietary tryptophan.⁸³ In developed countries, niacin deficiency may occur in malabsorption syndromes, such as Crohn

disease, anorexia nervosa, HIV, carcinoid syndrome, Hartnup syndrome, malnutrition secondary to alcoholism, and with use of medications including isoniazid, 5-fluorouracil, and 6-mercaptopurine.^{82,83}

Clinical Features

The clinical manifestation of niacin deficiency is pellagra. This is classically described in terms of the “three Ds”: dermatitis, diarrhea, and dementia. The dermatitis of pellagra is typically symmetric and in areas of sun exposure or friction. It tends to be erythematous and then hyperpigmented and scaly. A classic finding is the Casal necklace—a scaling, hyperpigmented dermatitis on the neck and chest. Bullous and depigmenting lesions also have been described,⁸³ as well as glossitis, stomatitis, and facial redness with a butterfly distribution.⁸²

Diagnosis and Treatment

Diagnosis of niacin deficiency is typically made after rapidly diminished clinical features with niacin supplementation, recommended at 50–100 mg/d.

Riboflavin Deficiency (Vitamin B₂)

Dermatologic manifestations:

Cheilitis, angular stomatitis, glossitis

Diagnosis:

Low plasma riboflavin levels

Treatment:

Riboflavin replacement

Niacin deficiency

Dermatologic manifestations:

Dermatitis of pellagra

Diagnosis:

Improvement after niacin replacement

Treatment:

Niacin replacement

Vitamin B₆ (Pyridoxine)

Vitamin B₆, or pyridoxine, is a water-soluble vitamin found in meats, bananas, and such vegetables as beans and potatoes. Deficiency in Western countries is typically seen in malnourished patients, chronic alcoholics, and patients taking isoniazid, penicillamine, or hydralazine.⁸²

Clinical Features

Pyridoxine deficiency manifests as perioral and perianal skin changes similar to those seen in vitadice.^{82,84} min B₂ or zinc deficiency, and may resemble seborrheic dermatitis, stomatitis, or glossitis. GI symptoms and neurologic symptoms (such as weakness, confusion, or peripheral neuropathy) may be seen, as well.^{82,84} Blepharoconjunctivitis and atrophic tongue also have been described.⁸⁸

Diagnosis and Treatment

Similar to that of other water-soluble vitamins, diagnosis can be made by serum levels, but may be made more commonly by prompt resolution of symptoms after treatment.

Pyridoxine Deficiency (Vitamin B₆)

Dermatologic manifestations:

Seborrheic dermatitis, glossitis, stomatitis

Diagnosis:

Low serum levels of pyridoxine

Treatment:

Pyridoxine replacement

Vitamin C

Vitamin C, or ascorbic acid, is a water-soluble vitamin found in many citrus fruits, vegetables, and organ meats. It is obtained exclusively in the diet, as humans are unable to synthesize vitamin C. Like the deficiencies of other water-soluble vitamins, vitamin C deficiency is rare in developed countries, and is found in conditions of general malnutrition, such as in patients with alcoholism and/or drug addiction and in rare socially isolated elderly patients.

Clinical Features

Deficiency of vitamin C causes the clinical entity of scurvy, with several classic cutaneous findings: follicular hyperkeratosis, perifollicular hemorrhages, and corkscrew-like, coiled hairs embedded in the hyperkeratotic follicular material. Also seen are petechiae and ecchymoses in dependent and friction-prone areas and swollen, inflamed gums (hemorrhagic hyperplastic gingivitis). Also seen in chronic vitamin C deficiency is a woody edema of the legs.^{89–91}

Diagnosis and Treatment

Serum levels of ascorbic acid fall to almost zero rapidly after failing to meet sufficient dietary requirements, limiting the diagnostic value of serum testing. Diagnosis is typically made on clinical grounds, such as with a patient having signs of scurvy, or with improvement of symptoms with supplementation of vitamin C. In addition to its role in treatment of clinical deficiency, vitamin C, along with zinc and arginine, has been associated with improvement in the treatment of pressure ulcers.⁹²

Vitamin C Deficiency

Dermatologic manifestations:

Hyperkeratosis, petechiae, ecchymoses, woody edema of the legs

Diagnosis:

Clinical improvement in symptoms with vitamin C replacement

Treatment:

Vitamin C replacement

Vitamin K

Vitamin K is a fat-soluble vitamin found in green leafy vegetables and legumes. It is also synthesized by bacteria in the digestive tract. Deficiency is seen in malabsorptive states, such as Crohn disease, pancreatic insufficiency, and with medications such as antibiotics, anticonvulsants, isoniazid, rifampin, and cholestyramine.⁸⁹ It is also seen in patients with liver disease and in patients with poor diet.

Clinical Features

Deficiency of vitamin K is manifested by coagulopathy caused by deficiency of vitamin K-dependent clotting factors II, VII, IX, and X. As a result, patients with deficiency in vitamin K present with coagulopathy, with easy bruising, ecchymoses, or bleeding from the GI or genitourinary tract, or with excessive bleeding after injury, trauma, or surgery.

Diagnosis and Treatment

Diagnosis is made with the appropriate history and clinical findings, along with prolonged prothrombin time. The coagulopathy of vitamin K deficiency can be corrected with oral or subcutaneous supplementation. Cases with severe bleeding may require parenteral vitamin K supplementation and possibly transfusion of fresh frozen plasma.

Vitamin K Deficiency

Dermatologic manifestations:

Easy bruising, ecchymoses

Diagnosis:

Prolonged prothrombin time

Treatment:

Vitamin K supplementation

VITAMIN TOXICITY

Potentially toxic levels of vitamins can be achieved easily in people who take very high potency vitamins. Water-soluble vitamins have an extraordinarily broad therapeutic ratio, with toxicity occurring only at doses thousands of times the daily value. Fat-soluble vitamins are generally more toxic than water-soluble vitamins. Table 31.3 summarizes some important points related to some vitamin toxicities.

Table 31.3 Toxicity of Commonly Used Vitamins

Vitamin	Clinical features of vitamin toxicity	Minimum daily dose associated with adverse effect ⁹³
Vitamin A	Liver toxicity, cirrhosis, birth defects, benign intracranial hypertension ^{93,94}	Cirrhosis: 25,000 IU Birth defects: 10,000 IU
Niacin (B ₃)	Flushing, nausea, vomiting, diarrhea, liver toxicity, fulminant hepatic failure (at least one case report) ⁹³	Flushing/gastrointestinal side effects: 10 mg Hepatotoxicity reported with 500 mg/d, but generally seen in doses >1000 mg/d
Vitamin B ₆	Sensory neuropathy, photoallergic drug dermatitis, acneiform eruption, contact dermatitis ^{93,95-97}	300 mg
Vitamin C	Nausea, abdominal cramping, diarrhea; reports of increased incidence of oxalate kidney stones have not been substantiated ^{93,98,99}	1000 mg

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Emergency management of skin torture and self-inflicted dermatoses

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Torture writ broadly is the intentional infliction of physical or psychologic pain.¹ The term includes a wide variety of conduct ranging from that instigated by authorities to gain confessions or information to that caused by private actors in the course of domestic abuse or in the intimidation of neighbors or disliked ethnic or religious minorities. Most legal definitions of torture, however, restrict its definition by requiring an element of state action; thus, for example, the United Nations Convention against Torture defines it as follows:

Any act by which severe pain or suffering, whether physical or mental, is intentionally inflicted on a person for such purposes as obtaining from him or a third person information or a confession, punishing him for an act he or a third person has committed or is suspected of having committed, or intimidating or coercing him or a third person, or for any reason based on discrimination of any kind, when such pain or suffering is inflicted by or at the instigation of or with the consent or acquiescence of a public official or other person acting in an official capacity. It does not include pain or suffering arising only from, inherent in or incidental to lawful sanctions.²

Similarly, the damage done by torture and the evidence of the same range widely. On the one hand, some persons torturing others seek to injure their victims in a way that is highly visible and consequently damaging to the victim's psyche (and serve as a threat to anyone who sees the victim). Cases in which perpetrators burn women chemically or thermally for failing to accept proposals or in defense of a family's "honor" will fall into this category. Such injuries can also lead to secondary complications such as skin infection and scar-related contractures. On the other hand, other forms of torture, although extremely painful and devastating to the victim, are expressly designed to leave no visible mark on the skin whatsoever, in large part to allow the torturer to deny the torture. Without in any way diminishing the severity, horror, and tragedy of the latter, this chapter focuses on the former in the context of addressing such injuries in an emergency situation.

CLINICAL AND LABORATORY AIDS REQUIRED FOR DIAGNOSIS

In most cases that will fall under the rubric of torture, an especially detailed dermatologic history should be performed, as the exact location and description of wounds and scars can prove significant both for treatment and further legal proceedings. The Istanbul Protocol, developed for UN investigations of torture, details extensively what an appropriate medical history and examination, including specifically that of the skin, should try to contain.³ Any history of skin disease and lesions that

predate the described torture should be noted. Lesions more consistent with torture will include those that are asymmetric, are irregular linear lesions, and have well-demarcated borders.⁴ All of this should be directed, in addition to providing treatment, to determining whether the physical findings on examination are consistent with a history of torture as presented.⁵ A thorough examination of all skin areas should be conducted to the extent permitted, as a patient may have passed out during an episode of torture and not even know all affected portions of his or her body. It should be noted that torture, from the point of view of skin damage, will tend to be most extensive, when the torturer did not expect that the patient would be leaving custody any time soon, if ever, and less so if a known court date or its equivalent had to be kept in the near future.⁶ The exception, of course, lies in those cases where the visible damage is meant to frighten others or permanently scar the victim. Additionally, although one might suspect that a person in the position of potential asylum seeker or victim seeking redress might seek to attribute every scar to torture, at least one physician who treats asylum candidates has noticed the exact opposite and that such victims tend to minimize rather than exaggerate.⁶ Patients who have been brutalized and shamed may also be reluctant to permit full examinations, and although the wishes of the patient must ultimately be respected, the limitations of such an examination need to be noted. Finally, photography, properly done, can provide invaluable documentation and should be strongly considered.

The type of torture inflicted is likely dependent on the country or circumstances in which the torture took place. Although no fully accurate statistics of torture methods exist, one study found, for example, that electrical burns were extremely common in Bangladesh but not present in Iran, whereas foot beatings were the rule in Bangladesh and Syria but largely absent in Peru and Uganda.⁶ A study of Sri Lankan victims showed that torturers beat nearly all victims with blunt weapons and burned 57% with cigarettes, whereas chemical and electrical burns, for example, were far less frequent.⁷ The point is, however, that the examiner may detect patterns and injury based on the country or location in which the torture occurred.

Probably, the most common form of injury in torture is that from blunt trauma, be it from stick, club, rod, or fist. Danielsen and Rasmussen⁴ provide an excellent review of the consequences and manifestations of this form of torture. From the dermatologic perspective, such beatings may result in lacerations, abrasions, ecchymoses, and edema, although it may be rare for a torture victim to present with the immediate aftereffects of such trauma. Consequently, unless a wound reaches full thickness, there may well be little evidence of the

trauma at the time the patient is brought to medical attention.⁸ Similarly, it can be difficult to determine the age of bruises from visual assessment only, although bruises in the elderly and chronically sun-damaged will likely persist longer.^{9,10} As is the case with suspected domestic abuse, it may be necessary to evaluate and document the trauma to the extent necessary to distinguish trauma from an accidental fall or other injury from more wanton and intentional violence (e.g., the custodial claim that the victim “simply fell” on his way out of the police car or “tripped” on his way into the interrogation room and hit his head on the table). Scars produced here will often appear nonspecific, although linearly patterned, hyperpigmented scars, such as from trauma from whippings or beatings with rods, may point strongly toward torture. Fingertip patterns of bruises, for example, suggest restraint.¹¹ Similarly, the tight binding of a victim around his or her arms or legs may produce characteristic linear scarring around the arms and ankles. In evaluating damage from possible blunt force with respect to scars, it must be kept in mind that a huge variety of causes can produce scarring throughout the body, from accidents at home and work and on playing fields to acne to earlier infections to stretch marks to vaccinations to prior surgery to ritual wounds, and although many of these scars are easily distinguished, it is not always the case; it is hard to tell if a kick to the legs came from torture or a soccer tackle.

The practice of *bastinado* (also known as *falaka* or *falanga*), the systematic beating of the feet, qualifies as a subset of blunt trauma and is another common torture with occasional dermatologic implications.¹² The practice is common among torturers, probably because it is easy to carry out, is exquisitely painful, and generally produces little visible injury; nonetheless, above and beyond the pain of walking due to trauma to the soles, cases of atraumatic necrosis of the toes and necrotic ulcers on the feet also have been reported. The necrosis is, in part, a consequence of the damage to the subcutaneous tissue pads of the feet that can no longer cushion them while a patient is walking or standing.^{5,13}

Moving along on the realm of blunt trauma, torturers will also often crush or remove nails, both due to the terrible pain such damage inflicts and due to the relatively minimal damage to the rest of the body. The consequence of such damage, after it heals, is a damaged nail bed that produces distorted nail growth, although such changes are not easy to distinguish from general nail trauma.⁶ A differential of such damage may include, for example, psoriatic nail disease.

The various forms of burning—be they thermal, chemical, or electrical—are the most likely types of torture to produce skin damage and changes. Direct application of heat with a metal rod will tend to cause a brand, resulting in a full-thickness burn that demonstrates the shape of the object that caused the damage, with a scar forming in that shape.

Cigarette burns are likely the most common source of skin damage from burning. They follow the damage patterns of burns on any scale, ranging from superficial burns akin to moderate sun damage to full-thickness burns of the dermis and epidermis, albeit in circular patterns of 5–20 mm in diameter, often uniform and with a rolled border.^{14,15} The damage caused will generally depend on the length of time the cigarette is applied to the skin, and may or may not be accompanied by a blister. The time needed to achieve the damage of a full-thickness burn is longer than the reflex time for withdrawal, indicating that such burns should be accompanied by a story of

the affected body part being held in place while the burn was inflicted. Such injuries will generally heal in weeks to months, depending on the depth of injury, but are at risk for secondary infection. Cigarette burns inflicted in the course of torture are more likely to be on surfaces of the body visible to the victim, as no small portion of the pain and trauma from such burns comes from witnessing the event. Torturers also often burn victims this way in tight patterns as opposed to haphazard and irregular burns.^{6,15} A differential diagnosis, depending on the case, may include impetigo, abscess formation, and pyoderma gangrenosum.

Chemical burns are an invidious form of torture, frequently associated with attempted disfigurement of a woman for refusal to marry or for some supposed disgrace visited on her family.¹⁶ Such torture has been reported in India, Pakistan, Bangladesh (Figures 32.1 through 32.8), and Uganda, where sulfuric acid is the most common agent. In most cases, the face is involved, as the goal of the torture is, in no small part, to render the victim permanently disfigured, in order both to render her socially unacceptable and to let the victim serve as a warning to others. When the burn is extensive, cosmetic surgery may have a role to play in ameliorating the damage, albeit not typically in the emergency context, although the sooner expert wound care and plastics are involved, the better the outcome.

Electrical burns can occur when a torturer attaches electrodes to various parts of a person's body and runs current through the circuit, although such burns are usually incidental to the torture intended rather than its aim. These burn marks are usually small circular lesions that leave fine scars, although the wound will depend on the type of current and attachment used. Danielsen and Rasmussen⁴ again provide an



Figure 32.1 Domestic violence manifested by acid burns due to 50% sulfuric acid being thrown on the victim.



Figure 32.2 Domestic violence manifested by acid burns due to 50% sulfuric acid being thrown on the victim.



Figure 32.3 Domestic violence manifested by acid burns due to 50% sulfuric acid being thrown on the victim.

excellent overview of these differences. Broadening the foci of charge entry and emergence through the use of gels will render these marks even harder to find, if they exist at all.⁵ A particular form of electrical torture, common in Peru and other parts of South America ("picana," involving a wand that delivers a high-voltage but low-current shock), leaves clusters of tiny lesions covered with brown crusts and sometimes surrounded by a small erythematous ring. A differential diagnosis of such lesions may include contact dermatitis.⁴ Biopsy and histologic examination can play a role in the investigation of electrical torture. In the case of electrical burns, recently inflicted damage may show deposits of calcium salts on cellular structures that accords with the flow of an electric current, while perhaps also showing signs of burn damage due to the heat produced by the current.⁴ One case series involving histologic examination of 11 patients seen after burns from defibrillation, however, showed no such evidence, implying that such evidence may be present less frequently.¹⁷ Another study of 11 patients who suffered



Figure 32.4 Domestic violence manifested by acid burns due to 50% sulfuric acid being thrown on the victim.



Figure 32.5 Domestic violence manifested by acid burns due to 50% sulfuric acid being thrown on the victim.

electrical fatalities (also not torture related) showed deposition of copper and iron on the skin in a significant number of histologic specimens from these patients, suggesting that staining for these metals might help to support a case of electrical torture.¹⁸

Sexual abuse and torture, which may come in unfortunately myriad forms, can also, although not always, leave physical signs. For acute victims of rape (within 72 hours), a "rape kit" or equivalent should be used to document evidence. Defensive bruising, injury to the posterior fourchette, fossa navicularis, labia, and vagina in women, and the anus



Figure 32.6 Post burn neck scar contracture.



Figure 32.7 Domestic violence manifested by acid burns due to 50% sulfuric acid being thrown on the victim.

in either sex, can all suggest sexual assault.¹³ Patients should also be evaluated for sexually transmitted disease with appropriate laboratory studies. Alternatively, a proper dermatologic examination should distinguish diseases, such as lichen sclerosis et atrophicus, psoriasis, contact dermatitis, and others, that often masquerade as sexual abuse.¹³



Figure 32.8 Domestic violence manifested by acid burns due to 50% sulfuric acid being thrown on the victim.

Torture can also potentially, as a result of stress, make a patient susceptible to flares of skin diseases from which he or she already suffers. Psoriasis and other diseases induced by various sorts of skin trauma may arise in response to torture via the Koebner phenomenon, while the psychologic stress of the same may either provoke urticaria¹⁹ or the uncontrolled repetitive self-rubbing that can exacerbate or introduce disease.⁴ Patients with other underlying diseases, such as diabetes mellitus and peripheral arterial disease, may also be more susceptible to ongoing effects from trauma to limbs and reduced healing. Patients who tend toward hypertrophic healing may develop keloids as a consequence of torture wounds. Finally, evidence of severe damage to the skin through torture may well indicate more internal damage that could result in rhabdomyolysis and consequently could warrant a check of renal function for signs of failure.²⁰

THERAPY

Patients with extensive skin damage due to chemical or physical burns should be referred to a burn unit and ultimately for appropriate surgical intervention, if necessary. Care is otherwise commensurate with the damages and normal wound care. Depending on the age of the skin damage and how it was inflicted, it is also important to look for signs of infection and to treat the same if discovered.

In almost every situation in which a patient was the possible victim of torture, thorough documentation of the history and examination becomes extremely important, whether for asylum claims or conceivable future legal actions against a perpetrator. In some cases and countries, for example, it is essential for a physician to identify the victim through specific means for any possible legal redress to follow. One U.S. study has found that individuals who received medical evaluations from Physicians for Human Rights have obtained asylum at statistically significant higher rates than have those without similar documentation.²¹

It is also important to ensure that social workers and psychiatrists or psychologists are involved in treatment when torture is suspected.¹⁴ Similarly, a physician dealing with a patient who is suspected of suffering or claiming to be the victim of torture should be treated with great care. No matter how much the physician wishes to help, a person who has just been utterly mistreated by an authority figure and has suffered

under questioning may be reflexively suspicious of answering the questions of a new authority figure. Women (and men) who may have been sexually brutalized may be ashamed to tell their whole story. Various forms of torture may also lead to impaired memory of the event. In any case, it may be necessary for additional visits for an adequate documentation of what has happened to the patient. Although these visits obviously should not take place in the emergency department setting, such a course of aftercare should be established to the extent possible.

COURSE AND PROGNOSIS

In cases of intentional mutilation, whether through chemical, electrical, thermal, or mechanical destruction of the skin, the patient's course and prognosis depend heavily on the extent of damage inflicted as well as the immediacy of appropriate wound care. Unless the patient was severely and significantly burned, most scars will follow a normal course of healing absent secondary infection or other complication. For the purposes of documenting torture, damage to the skin should be evaluated as near in time to the event as possible.

Of course, the goal of torture is ultimately not the infliction of the pain or disfigurement, per se, but the psychologic repression of the victim. As such, much treatment will lie beyond the expertise of the dermatologist and will depend on ongoing social and psychologic assistance. It is essential, therefore, that the patient does not simply shuttle through for evaluation of his or her skin condition.

The evaluation, depending on the situation, as noted previously, may be important for a patient's possible need or desire to seek asylum. All relevant symptoms should be documented, of course, and if there is no examination beyond the dermatologic that should be noted, lest evidence of the absence of such complaints be used against the patient. Even when treatment is being offered in situations where some limitations may be present in how far the patient may explain the torture (e.g., a prisoner brought in by his captors/torturers to seek medical treatment after a session of interrogation has gone too far) or the physician may express his or her opinions, documentation to the fullest extent, as well as an acknowledgment of any limitations, should be included.²² Similarly, a full examination for the purposes of an asylum claim likely may well lie beyond the purview and time constraints of the physician delivering emergency care, and arrangements for a more extensive examination by someone more familiar with medical (and legal) aspects of such claims is likely in order.²³

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Cutaneous signs of poisoning

Michael Joseph Lavery, Carolyn Stull, and Ronni Wolf

The skin is the largest organ in the body and the target for many manifestations of internal disease. Cutaneous poisoning disorders produce a myriad of clinical features. Poisoning, from whatever source, can be difficult to diagnose, and recognizing the cutaneous features can often be key to determining the diagnosis.

Features of poisoning may occur through inhalation, ingestion, or percutaneous contact of the poisonous substance. This may be accidental, self-induced (deliberate self-harm/suicidal), or through unintentional exposure.^{1,2} Early diagnosis and treatment are key in determining a successful clinical outcome; late presentation, severity of intoxication, and nonspecific presenting signs and symptoms are all compounding factors that make clinching a diagnosis difficult.

This chapter focuses on four major cutaneous poisoning syndromes: metallic poisoning (arsenic, mercury), β -carotene (carotenoderma), carbon monoxide (CO), and dioxin (chloracne) poisoning. Agent (Herbicide) Orange and its cutaneous effects are also discussed.

ARSENIC POISONING

Arsenic is a well-recognized poisonous metal due to its lack of odor, tasteless quality, and relative low cost. Arsenic contact may occur through smelting of metals, such as lead, copper, and gold. In smelting operations, as well as in the manufacture of pesticides and herbicides, contamination of the environment may be present, requiring extensive preventive measures. In the semiconductor industry for example, exposure to arsenic can occur during maintenance activities and especially during the handling of raw materials.

Chronic arsenic toxicity due to drinking arsenic-contaminated water is a major environmental health hazard. Many aquifers in various parts of the world, including in India, Taiwan, Bangladesh, and Northern China,³ are contaminated with arsenic. A recent survey in Bangladesh showed that around 20 million people are drinking arsenic-contaminated water, with documented arsenic levels being above the recommended safe water threshold.⁴ Although rare in children, arsenic poisoning has been reported in children as young as 1 year old.⁵

Clinical Manifestations

Arsenic poisoning features can be differentiated through its acute and chronic presentations. In acute poisoning, features include periorbital edema, a mildly itchy maculopapular intertriginous eruption, and acral hyperkeratosis with lamellar peeling. Mees lines—transverse 1–2 mm white fingernail bands depicting arsenic deposition—are clinically apparent after an incubation period of 2 months (Figure 33.1).⁶ They are broader in the pediatric population. Other cutaneous findings include urticaria, erythema multiforme, periungual pigmentation,

acral desquamation, morbilliform eruption, and postinflammatory hyperpigmentation.⁷ Chronic arsenic poisoning has two hallmark findings: hyperpigmentation and arsenic keratosis. The hyperpigmentation presents as raindrop-shaped dyspigmentation, diffuse dark brown papules and plaques or diffuse hyperpigmentation on the extremities and trunk. Depigmented macules/patches (leukomelanosis) may also be present.⁸ The keratoses may be simple or nodular. The simple variant presents as bilateral thickening of the palms and soles, while the nodular variant presents as small protrusions on the hands, legs, or feet.⁶ Patients may eventually develop in situ carcinoma (actinic keratosis, Bowen disease) or invasive cutaneous carcinoma (basal cell, squamous cell, merkel cell).⁹ There is an increased lifetime risk of bladder and lung carcinoma.¹⁰ Other chronic cutaneous findings include persistent folliculitis, and facial flushing. Melanosis may also occur, presenting as hyperpigmented patches in the nipples, axillae, groin, and other pressure points.¹¹ Figure 33.2 summarizes the main acute and chronic clinical findings.^{6,12} Systemic organ involvement may also occur in arsenic poisoning as highlighted in Table 33.1.^{10,12,13}

Management

Initial management revolves around removal of the environmental exposure. Serum and urine arsenic levels should be taken at first clinical encounter. Chelation therapy with dimercaprol has largely been replaced with 2,3-dimercaptosuccinic acid. (DMSA).¹² When arsenic carcinogenic effects are present, measured arsenic levels are minimal; therefore, chelation therapy may not be effective.¹⁴ Twenty-four urine measurements should be collected for monitoring treatment response. Nail and hair samples may also be useful in chronic exposure with pubic hair being preferable to scalp hair due to less external contamination and slower growth. Finally, there are reports that oral retinoids may be used as a chemopreventive measure.¹⁰

MERCURY

Mercury poisoning, although rare, is still the second most common cause of heavy metal poisoning.¹⁵ For nearly 3000 years, mercury and its derivatives have been utilized in the medical field (Table 33.2). Mercury remains a contaminant of water, either from the burning of coal from power plants or from the inappropriate disposal of lights, paints, or batteries.¹⁶ It then enters the human life cycle through consumption of seafood (Figure 33.3). The cytotoxic effect of mercury is through depletion of the thiol reserves in the mitochondria.¹⁷ Consumption of contaminated seafood with mercury was previously reported in Japan in 1960 (Minamata disease)¹⁸ and in Iraq (contaminated grain).¹⁹

Clinical manifestations may vary, depending on the type of mercury, method of administration, dose, duration of exposure,



Figure 33.1 Mees lines on the fingernails. (Courtesy of Louise Barnes, MB, FRCPI; Dublin, Ireland.)

and differing sensitivity to the metal. Mercury has three different forms—elemental (metallic), organic, and inorganic.

Elemental

Elemental mercury, also termed metallic mercury, is commonly found in dental amalgams and contaminated seafood but may also be found in latex paints, barometers, thermometers, lamps, and mercury switches. Pediatric patients are at a higher risk of poisoning, as they attain a higher body concentration.

Mercury vapor is readily absorbed through the pulmonary tract and oxidized to inorganic mercuric ions, which then bind with sulfhydryl groups¹¹ (Figure 33.3).

Elemental mercury will rapidly diffuse across the blood-brain barrier and the placental membrane. Gastrointestinal absorption through oral mercury ingestion is minimal and as such ingestion through this method is unlikely to yield any toxic effects. Elemental mercury may be deposited anywhere in the body including the kidneys, skin, thyroid gland, liver, and lungs.²⁰

In acute toxicity, there are three symptomatic stages. A flu-like prodrome initially ensues with myalgia, pyrexia, headache, and mouth and throat dryness. After 2 weeks, patients develop multiorgan involvement. Pulmonary manifestations include interstitial pneumonitis, pulmonary edema, and pulmonary failure. Gastrointestinal features are comprised of an oral metallic taste, thirst, constipation, nausea, and vomiting.²¹ Renal involvement, with features of nephrotic syndrome, has been reported.¹⁵ The third stage entails neuropsychiatric symptoms.²¹

Chronic exposure produces the triad of intention tremor, erethism (combination of increased emotional excitability, personality changes, irritability, memory loss, insomnia, drowsiness, depression, decreased self-control), and gingivitis. Cutaneous manifestations include a blue line identified across the gingiva, an erythematous papular eruption, and a lichenoid drug reaction.²²

Inorganic

Types of inorganic mercury include mercuric chloride, mercuric oxide, mercuric sulfide, ammoniated mercury, and phenylmercuric salts. Pesticides, germicides, and antiseptics may contain

Acute poisoning

Chronic poisoning

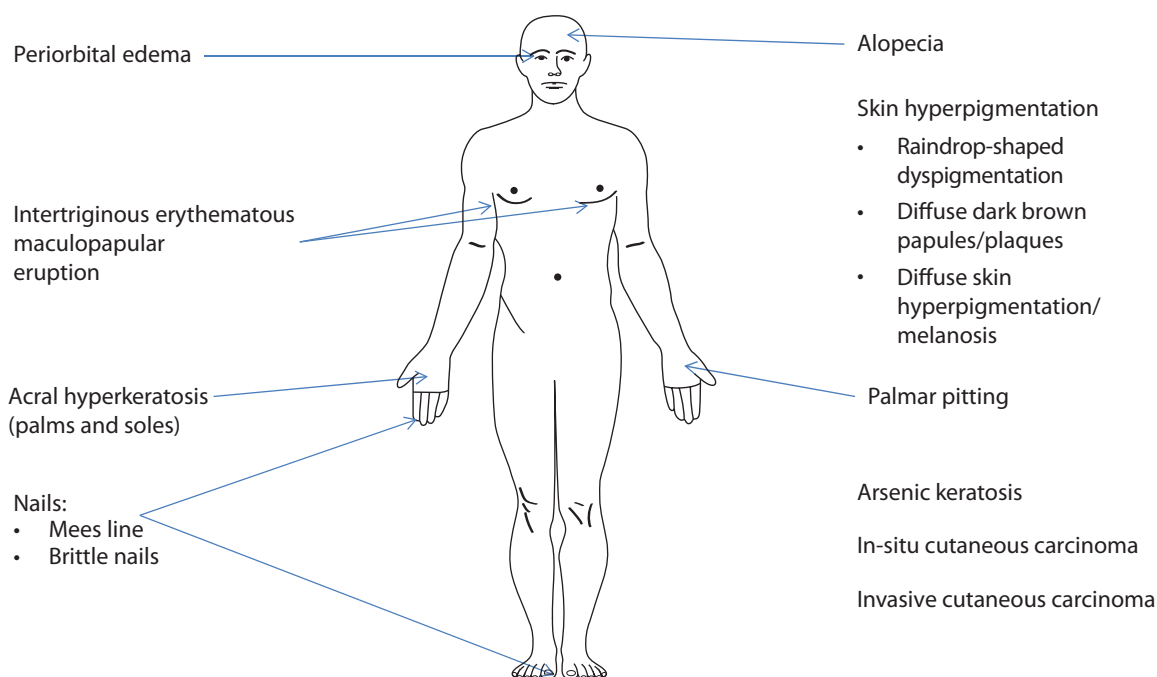


Figure 33.2 Acute and chronic clinical findings of arsenic poisoning.

Table 33.1 Other Features of Arsenic Poisoning

System	Manifestation
Neurological	Symmetrical sensory (axonal, large fiber; glove and stocking distribution) and motor (small muscles hand/feet) neuropathy Weakness, headache Encephalopathy Cognitive impairment Negative affect on intellectual function
Gastrointestinal	Colicky abdominal pain Nausea and vomiting Profuse watery diarrhea ("bloody rice water") Hypersalivation
Liver	Hepatomegaly; portal hypertension
Lung	Interstitial pulmonary fibrosis; pulmonary edema
Cardiac	Arrhythmias, cardiomyopathy, peripheral vascular disease
Hematological	Bone marrow suppression Hemolytic anemia
Malignancy	Skin—in situ carcinoma (AK, Bowen disease); invasive carcinoma (BCC, SCC, Merkel cell) Lung Genitourinary—renal bladder Gastrointestinal Hepatic
Other	Conjunctival congestion; edema of limbs

Note: AK, actinic keratosis; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

inorganic mercury. Although ingested inorganic mercury may be readily absorbed in the gastrointestinal (GI) tract (in contrast to elemental mercury), only around 10% of inorganic mercury undergoes systemic absorption. Inorganic mercuric salts target the gastrointestinal tract (nausea, vomiting, esophageal erosions, burning tongue, gingivitis) and the kidneys, leading to renal failure. Inorganic mercury vapor targets the neurologic system leading to tremor and dementia. Cutaneous manifestations include slate-gray pigmentation over areas of chronic exposure from mercury-containing creams (exogenous ochronosis).⁶ In addition, patients may develop a blue linear pigmentation on the gingivae and tongue, which should be considered a marker for systemic poisoning.

Organic

Different types of organic mercury include compounds, in which mercury is bound to structures containing carbon atoms: methylmercury, phenylmercuric salts, and ethylmercury, as well as thimerosal (Merthiolate) and merbromin (mercurochrome). The principal source of organic mercury is from fish. Irreversible neurologic damage occurs as organic mercury can cross the blood-brain barrier due to its lipid solubility.²³ Features include ataxia, muscle spasms, paresthesia, demyelination, mental retardation, and deafness. Other sites affected include the kidneys and liver. Cutaneous features, secondary to organic mercury poisoning, are rare and possibly nonexistent.¹⁶ Ethyl- and methylmercury may also cross the placenta and cause small birth weight and birth defects that lead to childhood seizures, mental retardation, chorea, tremors, athetoid movements, spasticity, deafness, and cataracts.

Table 33.2 Common Metal Sources of Exposure

Arsenic	Mercury
Occupational <ul style="list-style-type: none"> Smelting industry Mining industry Semiconductors Chemical plant Glass manufacturing Agriculture/factory worker (animal feed, pesticides, fertilizers) Painter Wine maker 	Occupational <ul style="list-style-type: none"> Mining industry Chemical/electrical engineering Incineration processes Agriculture
Nonoccupational <ul style="list-style-type: none"> Drinking water (deep water well) Food Chinese/Indian/Korean traditional medicine 	Nonoccupational <ul style="list-style-type: none"> Seafood—contaminated fish/shellfish Medicinal (dental amalgams, dermatologic creams/cosmetics) Medical devices—thermometer, sphygmomanometer Household devices—light bulbs, batteries Horticulture—fungicides, bactericides Electronic devices

Thimerosal (Merthiolate) is 49.6% ethylmercury²⁴ and was previously used as a vaccine preservative in the hepatitis B, diphtheria-tetanus-acellular pertussis, and some *Haemophilus influenzae* type B vaccines.^{25–27} There were reports of idiopathic autism induced by mercury exposure from vaccines which exceeded the U.S. Food and Drug Administration (FDA) safety limit of thimerosal. Although no cause-and-effect relationship to autism was ever confirmed, thimerosal has been removed from most childhood vaccines vial, although it is still used as a preservative in multidose vial flu vaccines.²⁸

Table 33.3 highlights the different forms of mercury.^{6,16,20,21,29,30}

SPECIFIC CUTANEOUS DISEASES

Mercury poisoning may cause certain cutaneous diseases. Acrodynia, also termed pink disease, was first reported in Australia in 1890.³¹ It was later realized that this condition was related to mercury exposure; its use in medications and teething powders was discontinued. Acrodynia is a hypersensitivity condition to inorganic mercury (mercury salt/calomel), principally affecting infants and young children. Early features include irritability, lethargy, and anorexia along with pink discoloration of the tips of the fingers, toes, and nose; the hands and feet later turning a dusky pink color. The hands become swollen and intensely painful (affecting sleep), with profuse sweating and desquamation, occurring later on in the disease process. Acrodynia is characteristically found in patients who have "puffy, pink, painful, paresthetic, perspiring and peeling hands."²¹ Itch may also be a feature, which can cause excoriations, lichenification, and even trichotillomania; pruritus should also be added to this characteristic descriptive alliteration. Due to the associated muscle hypotonia that also ensues, these children are able to assume the "salaam position" whereby they sit with the head between their legs, while rubbing their hands together in an attempt to alleviate the pain. The patients do not wish to stand or walk due to the muscle hypotonia. The natural course of the disease is prolonged with a delayed presentation, appearing to be a good prognostic sign. Mortality, however, is around 10%.³¹

Another cutaneous disease associated with mercury poisoning is Baboon syndrome. Recently, a change in the nomenclature has been proposed, advocating that the disease be

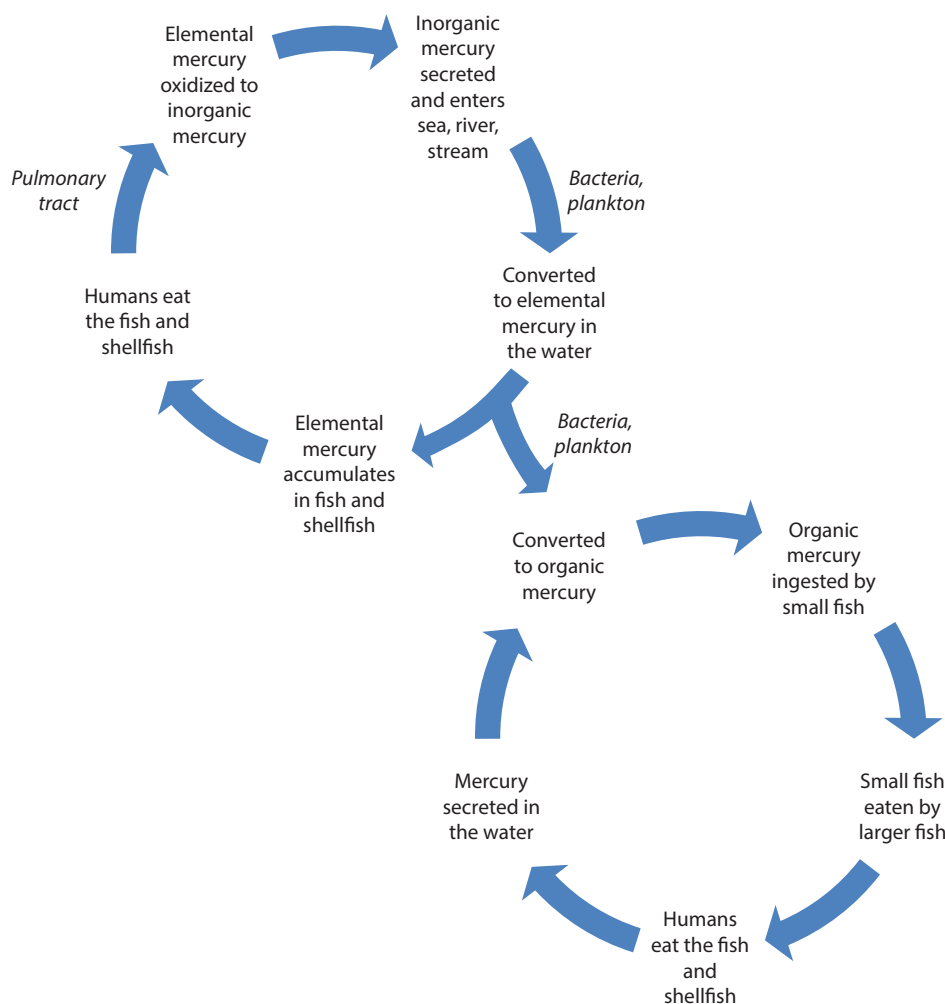


Figure 33.3 Cyclical interaction of inorganic, elemental, and organic mercury.

termed symmetrical drug-related intertriginous flexural exanthema (SDRIFE).³² Confirmation of the diagnosis includes five criteria: (1) exposure to a systemically administered drug at the time of first or repeated doses, (2) well-demarcated erythema of the gluteal/perianal area, and/or V-shaped erythema of the perigenital/inguinal area, (3) involvement of other flexural/intertriginous folds, (4) symmetry of affected areas, and (5) absence of systemic features.³²

Acute generalized exanthematous pustulosis (AGEP) has also been reported.³³ It presents with an acute eruption of widespread nonfollicular pustules with underlying edematous erythema. Fever and leukocytosis are also present. It is frequently associated with antibiotics (e.g., penicillins, macrolides). Although it may occur with mercury exposure, there is no definite conclusion of a cause-and-effect relationship. A new cutaneous sign of mercury poisoning has been found in 11 patients, who had recently increased their dietary seafood consumption and presented with features of small (1–2 mm), discrete, flesh-colored to slightly erythematous papules and papulovesicles.¹⁶ The lesions started to clear on complete withdrawal of seafood. Although guidelines state mercury toxicity generally occurs when serum levels are $>15 \mu\text{g/L}$,¹¹ one patient in the case series had a serum mercury

level of $6 \mu\text{g/L}$, indicating that mercury toxicity features may occur even at lower serum mercury values.¹⁶

Other associated cutaneous conditions include mercury exanthema and contact dermatitis. Despite mercury-containing creams being used for skin whitening purposes, it may paradoxically cause cutaneous hyperpigmentation. Finally, cutaneous granulomas may develop from unintentional or deliberate injection of mercury into the skin (e.g., Munchausen syndrome). Embolization to internal organs may ensue, leading to multiorgan failure.²¹

Table 33.4 summarizes the main cutaneous conditions and the associated clinical features.^{6,21,32}

Investigations

Mercury intoxication can be identified with mercury-level assays from both blood and hair. Serum levels are useful in recent exposure,³⁴ as well as in determining if the exposure was to the organic form (high blood-to-plasma ratio of up to 20:1) or the inorganic form (ratio of 1:1 to 2:1).³⁵

Hair mercury measurement is a reliable method to test for chronic methylmercury exposure over the past 2–3 months. Hair contains an amino acid group, which has high sulfhydryl

Table 33.3 An Overview of the Different Mercury Forms

Different forms of mercury	Elemental (metallic)	Organic	Inorganic
Type	Mercury vapor Earth's crust Atmospheric	Methylmercury—converted to elemental mercury in the brain Ethylmercury Thimerosal (49.6% ethylmercury) Alkyl mercury	Mercury vapor—most common source Divalent mercury salt—most toxic source Converted to elemental mercury in water
Source	Dental amalgams Seafood Thermometers Lamps Mercury-laden latex paint Cutaneous	Seafood (alkyl mercury) Multidose vial influenza vaccines (thimerosal) Plastics, paper Processed wood Insecticides	Skin whitening products; antiseptic facial creams; bleaching creams Lamps Wood preservatives Pesticides, germicides
Half-life	60 days	45–70 days	42 days
Absorption	Respiratory tract (oxidized to inorganic mercury at alveoli) Limited GI absorption	GI tract ($\geq 95\%$) Respiratory tract (80%)	Respiratory tract GI tract (2%–10%) Skin (3%–4%)
Pharmacokinetic distribution	99% circulates in <ul style="list-style-type: none"> • Blood (plasma protein, glutathione, metallothionein bound) • RBC (Hb bound) 	99% circulates in <ul style="list-style-type: none"> • Blood (plasma protein, glutathione, metallothionein bound) • RBC (Hb bound) 	99% circulates in <ul style="list-style-type: none"> • Blood (plasma protein, glutathione, metallothionein bound) • RBC (Hb bound)
Excretion	Predominantly urine Feces	Predominantly feces (90%) Urine (< 10%)	Urine and feces Also sweat, breast milk, saliva, tears
Clinical features	Acute <ul style="list-style-type: none"> • Flu-like prodrome • Pulmonary, GI, renal, CNS and GU involvement • Neuropsychiatric symptoms Chronic <ul style="list-style-type: none"> • Triad: intention tremor, gingivitis, erethism 	Neurological <ul style="list-style-type: none"> • Ataxia • Demyelination • Autonomic dysfunction • Mental retardation • Cerebral palsy Birth defects	Gastrointestinal <ul style="list-style-type: none"> • Esophageal erosions • Gingivitis • Burning tongue Renal failure Neurological <ul style="list-style-type: none"> • Tremor • Dementia
Cutaneous features	Blue line across gingiva Lichenoid reaction Erythematous papular eruption	Rare or nonexistent	Acrodynia Blue line across gingiva and tongue (marker of systemic poisoning); stomatitis Slate-gray pigmentation (exogenous ochronosis)
Principal organs affected	Kidney Brain Placenta	Brain Kidney Placenta	GI tract Kidney Liver—periportal area
Treatment	Chelation <ul style="list-style-type: none"> • DMSA (PO) • D-penicillamine (PO) 	Chelation <ul style="list-style-type: none"> • DMPS (IV/PO) • DMSA (PO) • Note: no FDA approval to treat methylmercury or ethylmercury poisoning with chelation therapy 	Chelation <ul style="list-style-type: none"> • DMPS (IV/PO) • DMSA (PO) • D-penicillamine (PO)

Note: $\mu\text{g/L}$, microgram per liter; CNS, central nervous system; DMPS, 2,3-dimercaptopropane sulfonate; DMSA, 2,3-dimercaptosuccinic acid; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; GU, genitourinary; Hb, hemoglobin; IV, intravenous; PO, per os (oral); RBC, red blood cell.

content,²⁹ and mercury binds with the sulfhydryl compounds.¹¹ Although hair may be exposed to environmental contamination and potentially distort analysis, it is still felt to be a reliable measurement of mercury analysis.²⁹ The World Health Organization set a limit of 1 mg/kg of hair mercury concentration; however, moderate mercury poisoning hair concentrations range from 200–800 mg/kg.²⁹

Urine mercury can be useful in determining the quantity of mercury exposure, with significance placed on the different mode of excretion of each form of mercury (Table 33.3). Organic

mercury, for example, is mainly excreted through feces, and therefore, determining urine mercury concentration after exposure to this form, is of limited clinical value. Although metallic mercury is excreted mainly in the urine, complications from oral ingestion are rare, due to its limited gastrointestinal absorption. Measurement of urine mercury concentration is useful, if the patient has been exposed to inorganic mercury. In acrodynia (pink disease), inorganic mercury inhibits the catechol methyltransferase enzyme, leading to increased urinary levels of vanillylmandelic acid (VMA) and homovanillic acid (HVA).³⁶

Table 33.4 Distinct Cutaneous Syndromes Associated with Mercury Poisoning

Cutaneous diseases	Features
Acrodynia (pink disease)	<p>Dermatologic</p> <ul style="list-style-type: none"> • Pink, puffy, painful, (pruritic) paresthetic, perspiring, peeling hands • Involvement of the feet, tip of the nose, and cheeks • “Salaam position” (sit with head between the legs while rubbing both hands) • Cold and moist skin • Excoriations, lichenification • Trichotillomania causing alopecia • Erythematous and swollen gingivae from excessive salivation • Oral mucosal ulceration; tooth loss • Nail loss <p>Other</p> <ul style="list-style-type: none"> • Hypertension, tachycardia • Photophobia • Pelvic girdle and pectoral muscle hypotonia
Acute generalized exanthematous pustulosis (AGEP)	<p>Dermatologic</p> <ul style="list-style-type: none"> • Widespread nonfollicular pustules with underlying edematous erythema <p>Other</p> <ul style="list-style-type: none"> • Pyrexia • Leukocytosis
Baboon syndrome/SDRIFE (symmetrical drug-related intertriginous and flexural exanthema)	<p>Dermatologic</p> <ul style="list-style-type: none"> • Diffuse, well-demarcated, symmetrical, erythematous maculopapular eruption of the gluteal/perianal area, intertriginous/flexural folds • V-shaped pattern of the inguinal/perigenital area
Mercury exanthema	<p>Dermatologic</p> <ul style="list-style-type: none"> • Diffuse, symmetrical erythema affecting the flexural and proximal extremities; associated pruritus and burning • Nonfollicular sterile pustules • Purpura • Desquamation during resolution at around 2 weeks postexposure <p>Other</p> <ul style="list-style-type: none"> • Fever, malaise • Polydipsia
Contact dermatitis	<p><i>Acute contact dermatitis</i></p> <ul style="list-style-type: none"> • Swelling, vesicles, scaling, irritation <p><i>Tattoo reaction</i> (red pigment from mercuric sulfide)</p> <ul style="list-style-type: none"> • Localized swelling and scaling at site of tattoo • Psoriasiform verrucous reaction <p><i>Dental amalgam reaction</i></p> <ul style="list-style-type: none"> • Brown to violaceous papules and plaques; usually adjacent to the dental amalgam
Hyperpigmentation	<p>Dermatologic</p> <ul style="list-style-type: none"> • Slate-gray pigmentation of the treated skin • Mercurialities—discoloration of the lens from prolonged periocular cream application
Cutaneous granuloma	<p>Dermatologic</p> <ul style="list-style-type: none"> • Flesh-colored to erythematous granulomatous lesion at site of exposure <p>Other</p> <ul style="list-style-type: none"> • Visceral organ involvement: lungs, kidneys, liver, spleen

Treatment

A detailed history (including an occupational history) and a thorough physical examination will aid in developing the management plan. Diagnosis of mercury poisoning is difficult, and as such treatment initiation may be delayed. Removal of the patient from the source of mercury is imperative. Clothing should be destroyed, and patients should wash thoroughly with soap and water. Eyes may be irrigated with normal saline.

For symptomatic patients and those with toxic serum and urine levels, chelation therapy may be offered for inorganic mercury poisoning. Dimercaprol is rarely first-line therapy due to its adverse neurotoxic profile and is no longer the therapy of choice.²¹

2,3-Dimercaptosuccinic acid (DMSA) and dimercaptopropane sulfonate (DMPS), analogs of dimercaprol, may be employed. Due to its stability, DMPS is usually given

intravenously; however, when taken orally it has a greater absorption than DMSA. Despite this, DMSA has been shown to be more effective in animal studies at removing methylmercury from the brain.²⁹ The dose of chelation therapy varies among individual practices and clinical experience; however, DMPS is generally commenced at a dose of 5 mg/kg orally, administered every 6 to 8 hours; DMSA is commenced at an initial dose of 10 mg/kg (oral/intravenous) every 8 hours, decreasing to 12 hourly, later on in the dosing schedule.²⁹

Despite this, while DMPS is used as chelation therapy in many countries, it does not have FDA approval for use in the United States.³⁷ Furthermore, no chelation agents have FDA approval for the treatment of methylmercury or ethylmercury poisoning.²⁹

Other management options include D-penicillamine (a water-soluble derivative of penicillin) and chelation

combination therapies (which may have better clinical outcomes as compared to monotherapy).³⁸ Other therapies in the armamentarium include hemodialysis, peritoneal dialysis, and plasma exchange.

CAROTENODERMA

Carotenoderma is a phenomenon characterized by orange discoloration of the skin, which occurs as a result of carotene deposition in the stratum corneum. This entity is caused by excess ingestion of carotene, and is observed alongside carotenemia, or increased plasma levels of β -carotene.³⁹

Carotenoderma was first described in the early twentieth century in a subset of diabetic patients who were under strict dietary guidelines.⁴⁰ Shortly thereafter, this phenomenon was also reported in infants. In subsequent years, epidemics of carotenoderma have occurred in association with carotene-rich diets. During the Second World War, carrots were consumed in excess due to widespread availability and affordability in the midst of food rationing. Consequently, carotenoderma was observed, and determined to be transferable to infants through breastfeeding.⁴¹ During the 1970s, carotenoderma occurred in Japanese children who consumed an excessive number of tangerines or glasses of tangerine juice.⁴² Carotenoderma has also been observed in West Africa in association with ingestion of red palm oil, which is rich in carotenoids.⁴³

Carotenoids are found in a variety of fruits and vegetables and are responsible for their orange color. Green vegetables, including lettuce, also contain β -carotene; however, the presence of chlorophyll masks β -carotene-derived pigment. The β -carotene is accumulated exclusively through exogenous consumption and cannot be endogenously synthesized. Approximately one-third of ingested β -carotene will be absorbed. Absorption is contingent on the amount of fiber present, as well as the preparation process used.⁴⁴ The β -carotene is liberated during cooking, mashing, and pureeing of foods, thereby enhancing its absorption.

Carotenoids are absorbed through passive diffusion in the form of micelles. Once absorbed, β -carotene is converted into retinal by the enzyme 15-15'-dioxygenase within small bowel enterocytes. Retinal is subsequently converted to retinol (vitamin A) by retinal reductase.³⁹ Retinol is assembled into chylomicrons and transported to the liver and adipose tissue for storage.

Clinically, carotenoderma presents as yellow or orange pigmentation that has a predilection for acral skin surfaces including the palms, soles, nasolabial folds, and the tip of the nose. Carotenoderma may be distinguished from jaundice by the lack of scleral and oral cavity involvement. Additionally, while jaundice is accentuated by natural light, carotenoderma is more pronounced in artificial light.⁴⁵ Pigmentation will occur once serum levels of β -carotene exceed 250 $\mu\text{g/dL}$, and it often manifests 4–7 weeks after a carotene-rich diet has been initiated.⁴²

Histologic evaluation typically reveals concentrated carotene pigment in the stratum corneum. On direct immunofluorescence, carotene pigment will autofluoresce and may resemble the pattern observed in pemphigus vulgaris.⁴⁶

Carotenoderma is typically caused by excess dietary ingestion of carotene-rich foods, such as carrots, squash, sweet potato, pumpkin, beans, egg yolks, corn, and yams. Rare cases of carotenoderma may occur in association with diabetes mellitus, nephrotic syndrome, and hypothyroidism.^{47,48} Carotenoderma can also result from relative or absolute

deficiency of the enzyme 15-15'-dioxygenase, which impairs the conversion of β -carotene into retinal.⁴⁶

Although carotenoderma is generally considered to be a benign condition, there have been reports of weakness, weight loss, hepatomegaly, and amenorrhea with long-term adherence to carotene-rich diets.^{49,50} Notably, the conversion of β -carotene to vitamin A occurs at a pace too slow to cause hypervitaminosis A. Coloration can be expected to normalize within 2–6 weeks of return to a normal diet.⁴³

CARBON MONOXIDE POISONING

Carbon monoxide (CO) is a colorless, odorless gas. It has a 200-fold affinity for hemoglobin and combines to form carboxyhemoglobin.⁵¹ This causes a leftward shift in the oxygen-dissociation curve; therefore, less oxygen is readily released to tissues and organs, ultimately resulting in cell hypoxia and death. Poisoning occurs when the CO level is >3% in nonsmokers, and >10% in smokers. Exposure may occur from fireplaces, fuel-burning devices, or charcoal grills. Over five hundred deaths are attributed to CO poisoning annually in the United States,⁵² making CO alarms a regulatory requirement in many states.⁵³ CO may also be formed from liver metabolism of methylene chloride, a component of aerosol propellants and paint strippers.⁵¹

The symptoms of CO poisoning may be vague and mimic flu-like symptoms or other diseases. The features can be classified into mild, moderate, and severe, with the heart and the brain being the principal organs affected. In mild disease, carboxyhemoglobin level <30%, symptoms include headache, dizziness, drowsiness, confusion, fatigue, muscle jerks, palpitations, and nausea and vomiting. In moderate poisoning, levels 30%–40%, patients develop shortness of breath, chest pain with tachycardia, and tachypnea. In severe cases, levels >40%, features include palpitations, arrhythmias, hypotension, confusion, seizures, paralysis, and coma.⁵⁴

Given the nonspecific symptoms, cutaneous signs can aid in determining the diagnosis. Patients may develop cherry red discoloration of the skin, lips, and mucous membrane. The nails may exhibit a pink discoloration, changing to a dark blue-red color at postmortem.⁵⁵ Mees lines, also identified in arsenic poisoning, may be present. There may be areas of erosion and loss of curvilinearity of the fingernail bed border, which may completely resolve within 8 weeks.⁵⁴ Other features include erythema, vesicles, or bullae. Scalp edema and erythema may evolve into areas of alopecia.⁵⁶

Although clinical practice has dictated that this investigational method should be performed from arterial blood, an anticoagulated venous blood sample, which does not need to be sent on ice, has been shown to provide similar accuracy, along with less patient discomfort.⁵⁷ Pulse oximetry is not a reliable method of determining oxygen saturation status, due to its inability to distinguish between oxy- and deoxyhemoglobin.

Treatment involves high flow oxygen for up to 6 hours, although carboxyhemoglobin levels decrease at around 80 minutes postexposure.⁵⁴ Hyperbaric oxygen may also be employed and reduces carboxyhemoglobin levels in 22 minutes.⁵³

DIOXIN POISONING

Chloracne is an acneiform eruption that manifests as a result of dioxin poisoning. Dioxins are a group of polyhalogenated aromatic hydrocarbons that are formed as by-products in manufacturing processes that utilize chlorine. These processes

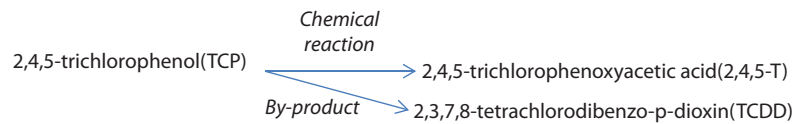


Figure 33.4 Formation of 2,4,5-T and the dioxin by-product TCDD.

include the production of herbicides, and consequently, dioxins may be found as contaminants in soil and water.⁵⁸ TCDD, chemically known as 2,3,7,8-tetrachlorodibenzoparadoxin, is the most toxic chemical in this class.

Small amounts (15–45 units per gram of blood fat) of TCDD may be incidentally found in Americans and Europeans due to dietary exposure. TCDD may be ingested by livestock or fish, stored in fatty tissue, and conveyed to humans upon consumption; however, incidental dioxin consumption in the United States and Europe has decreased in recent decades due to environmental regulations.

Acute dioxin toxicity has been rarely reported, and typically occurs as a result of an industrial accident. The most common adverse effect of acute dioxin poisoning is liver damage. Other reported effects include headache, conjunctivitis, hypertriglyceridemia, thrombocytopenia, diarrhea, and polyneuropathies.⁵⁹ Chloracne is the most sensitive indicator of excessive dioxin exposure, but other cutaneous manifestations may include porphyria cutanea tarda and hyperpigmentation.

The most notorious case of dioxin toxicity occurred in 2004 when the then Ukrainian presidential candidate, Viktor Yushchenko, was poisoned at a dinner party in London. His initial symptoms were headache and gastrointestinal upset, and within 5 days he was unable to walk. Blood tests at that time revealed leukocytosis, elevated liver enzymes, and TCDD concentrations of 100,000 units per gram of blood fat.⁵⁸ Weeks later, his face erupted with confluent acneiform nodules and cysts, the classic presentation of chloracne.

Dioxin is stored in fatty tissue and is eliminated slowly over a period of several years. A study conducted in Seveso, Italy, 20 years after an acute exposure incident revealed persistent, elevated plasma concentration of TCDD. In addition, the study found a strong correlation between plasma TCDD and the presence of chloracne.⁶⁰ Dioxin is excreted by the sebaceous glands, which induces the formation of comedones, nodules, and cysts. Facial involvement is characteristic, but involvement of the postauricular, axillary, and inguinal regions may occur. Involvement of the trunk and genital region may be seen in severe cases. Histopathologic findings include widespread prevalence of small infundibular cysts, with central collections of eosinophilic laminated or granular sebum.⁶¹ The widespread involvement of nearly every vellus hair follicle differentiates chloracne from acne vulgaris.

Chloracne poses a therapeutic challenge. While some lesions will resolve spontaneously, others may persist for decades. Topical and oral retinoids have been employed with some success. Olestra, a lipophilic dietary fat substitute, has been shown to increase intestinal excretion of TCDD, thereby reducing its elimination half-life from 7 years to 1–2 years.⁶²

AGENT ORANGE

Agent Orange, given its name by the orange-colored stripes on the side of the container barrels, was a herbicide used

during the Vietnam War from 1962 to 1971. It contained a 1:1 mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T).⁶³ Its main function was to destroy crops, which were both a food source and a means of enemy cover.

2,4,5-T is generated from 2,4,5-trichlorophenol (TCP) during chemical manufacturing; however, contamination, through generation of by-products of this chemical reaction, may occur, for example, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).⁶³ Figure 33.4 highlights this chemical process. TCDD is a form of polychlorinated dibenzodioxin (PCDD), an organochlorine.⁶⁴

TCDD and other dioxins are highly toxic compounds, which can affect many organs including the skin. Chloracne is the main skin manifestation from dioxin exposure. This can be differentiated from other forms of acne due to the predominance of closed comedones and the lack of inflammation.⁶⁵ Other documented cutaneous conditions include cutaneous lymphoma, soft-tissue sarcomas, and porphyria cutanea tarda.⁶³ Infamous exposures to dioxins include the assassination attempt of Viktor Yushchenko in September 2004,⁶⁶ as well as the large-scale release of dioxin from the ICMESA chemical plant in Meda, Italy, in July 1976 (the Seveso disaster).^{67,68}

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Cosmetic complications

Marina Landau, Ronni Wolf, and Natalie Curcio

Dermatologists have performed surgery and cosmetic invasive procedures on the skin since the nineteenth century. They are responsible for developments in chemical peels, hair transplantation, dermabrasion, sclerotherapy, laser surgery, and liposuction. As with any medical treatment, such procedures carry inherent risk for possible complications.

"If you've been thinking of having your face or body rejuvenated, but have been scared off by the thought of major surgery, then maybe it's time to think again. A wealth of new techniques and technologies have transformed the field of cosmetic treatment. The common feature of all these new treatments is 'minimally invasive'—that is, less cutting, less open surgery, less risk and less downtime. For individuals who choose a minimally invasive cosmetic procedure aimed at improving their overall appearance, fighting the signs of aging, and restoring their youthful features, any side effect is considered a "complication of an aesthetic treatment;" therefore, we have titled this chapter, "Cosmetic complications."

SCARRING

A significant number of procedures in dermatology carry a risk of scarring. In some procedure, scarring is inevitable, such as in surgical rhytidectomies and hair transplantations, whereas in others scarring is considered a complication, such as in chemical peels or laser surgery. The ultimate goal of a physician performing these interventions is to create a superior cosmetic outcome by avoiding or minimizing the scar.

Unfortunately, some cases result in hypertrophic scarring or keloids instead of a minimal scar. Those abnormally thickened scars are often painful or pruritic. The common locations for keloids and hypertrophic scars are on the upper portion of the trunk, neck, and arms and over bony prominences of the face. Factors predisposing to the formation of such scars include race (i.e., skin of color and Asian), heredity, excessive wound tension, excessively deep dermal injury, wound infection, and foreign body reaction. The concomitant or recent use of oral vitamin A derivatives had been traditionally considered as a risk factor for bad scarring,^{1,2} and this opinion is now challenged.^{3,4}

Despite the high prevalence of keloids in the general population, they remain one of the more challenging dermatologic conditions to manage. Because patients with a previous personal or family history of keloids are at increased risk for developing abnormal scars, they should avoid elective cosmetic procedures with a risk for scarring. If such a procedure is performed, wounds should be closed with minimal tension, and the immediate use of silicone gel sheets should be started.

A wide range of therapies exists for keloids, with the most commonly used modalities being intralesional steroid injection,

surgical excision, cryotherapy, laser therapy, radiation therapy, and the application of silicone gel sheets. Other treatments that have been used with variable success rates include imiquimod, 5-fluorouracil, bleomycin, retinoids, calcium channel blockers, mitomycin C, and interferon- α 2b. A meta-analysis of 39 studies, representing 27 different treatments, reported a 70% chance of clinical improvement with any type of treatment.⁵

INFECTIONS

Because dermatologic procedures disrupt skin integrity, they alter the body's protective barrier and predispose theoretically to cutaneous infections. Surprisingly, postoperative wound infections seldom complicate dermatologic procedures, ranging from 1% to 3%⁶; however, they have been rarely reported to complicate simple procedures, such as excisions, biopsies, skin grafts, chemical peels, dermabrasion, laser resurfacing, liposuction, blepharoplasty, and filler injections.

Antimicrobials continue to be widely used in the setting of dermatologic surgery for the prevention of surgical wound infection, endocarditis, and late prosthetic joint infections. Debate regarding routine use of topical and systemic antibiotics is still ongoing. The literature suggests that, for most routine skin procedures, antimicrobial use is probably not warranted. During prolonged Mohs procedures, delayed repairs, grafts, or any procedure that breaches a mucosal surface, decisions should be made on a case-by-case basis. Systemic prophylactic antimicrobials for laser resurfacing and liposuction are also not routinely necessary.⁷ For the prevention of surgical site infections, antimicrobials may be indicated for procedures on the lower extremities or groin, for wedge excisions of the lip and ear, skin flaps on the nose, skin grafts, and for patients with extensive inflammatory skin disease.⁸

Pooled data from four studies on the risk of bacteremia during dermatologic surgery including scalpel excision, electrodesiccation and curettage, Mohs surgery, hair transplantation, and flaps and grafts on clinically noninfected skin revealed a risk of bacteremia at 1.9%.⁹⁻¹² Despite a strong shift away from administration of prophylactic antimicrobials in many dermatologic surgery settings, it is still needed for patients with high-risk cardiac conditions and for a defined group of patients with prosthetic joints at high-risk for hematogenous total joint infection.⁸

BLEEDING

Although the overall incidence is low, bleeding complications in dermatologic surgery can occur and be the source of patient morbidity, particularly with the increased use of blood thinners especially among the elderly population. In addition, many patients may take dietary supplements that could alter coagulation.¹³ When these patients need to

undergo cutaneous surgery, the surgeon might encounter a problem of increased bleeding tendency. Discontinuation of these medications may increase the risk of cerebral and cardiovascular complications; therefore, a question of safe continuation or discontinuation of anticoagulant and antiplatelet medications before surgery might be a major issue in dermatologic surgery.

Metaanalysis of controlled studies reporting bleeding and other complications among patients undergoing cutaneous surgery who were taking anticoagulant medications suggests that although low, the risk of bleeding among anticoagulated patients may be higher than baseline.¹⁴ More recently, discontinuation of anticoagulation and antiplatelet therapy before surgery may not be the rule.

In recent years, dermsurgeons have been more likely to continue medically necessary aspirin and warfarin, but to discontinue prophylactic aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and vitamin E.^{15,16} There are no studies in the literature that examined the effects of combination anticoagulant therapy or the effect of herbal agents on postoperative risk of bleeding.

Since 2010, a new group of anticoagulants have emerged. The target-specific oral anticoagulants (TSOACs), which include dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis), are changing the way we manage not only thromboembolic disease, but dermatologic surgery for patients on these medications. Pradaxa is a direct thrombin (factor IIa) inhibitor, whereas Xarelto and Eliquis are factor Xa inhibitors. The perioperative management of patients on these anticoagulants is based on limited evidence, but the current recommendation for patients with normal renal function who need to undergo surgery is to stop the TSOACs 1 day prior to surgery for areas of low bleeding risk and 2 days prior to surgery for areas of high bleeding risk. TSOACs have a rapid onset of action and can be restarted at therapeutic doses at 24 hours after low-bleeding procedures and 48–72 hours after a procedure of high bleeding risk. Unlike heparin or warfarin, TSOACs do not have specific reversal agents.¹⁷

PROCEDURE-SPECIFIC COMPLICATIONS

Dermal Fillers

In 1899, Robert Gersuny, a Viennese surgeon, introduced mineral oil (Vaseline) for correction of soft-tissue defects. The principle of the technique consisted in the injection of a product that becomes semiliquid by heating but solidifies when cooled. Later, Vaseline was replaced with paraffin. Although serious complications were reported, it remained popular for the first 20 years of the twentieth century. Unfortunately, even with initial good results, secondary or late severe complications appeared due to the dispersion of paraffin. There was formation of nodules, the paraffinomas that were very difficult to remove. The sequelae of paraffin injections were observed for several years.¹⁸

Since that time, soft-tissue augmentation, using autologous or synthetic products, has become the cornerstone of facial beautification and of antiaging treatment. The choice of commercially available dermal fillers is growing constantly.^{19,20}

In the European Union, injectable fillers are certified as medical devices. Depending on the potential risk of each substance, a controlled clinical trial may be performed during the certification process; nevertheless, the process is

completely different from that applied for U.S. Food and Drug Administration (FDA) approval. Not infrequently, the safety and efficacy of many CE-certified injectables are assessed only in the postmarketing process.

No matter what the origin of the fillers is, they are usually classified into resorbable and permanent groups. Resorbable materials, such as collagens and hyaluronic acids, are removed from the tissue by phagocytosis. Permanent fillers, such as silicone and Bellafill (formerly known as ArteFill), cannot be removed efficiently. Large microspheres of nonresorbable fillers are encapsulated with fibrous tissue and escape phagocytosis.

In 2004, a new classification of dermal fillers, taking into account the long-term safety and reversibility of the side effects, was proposed.²¹ According to this classification, dermal fillers are nonpermanent and biodegradable (e.g., collagens and hyaluronic acids), semipermanent and biodegradable (e.g., poly-L-lactic acid), permanent and reversible (e.g., expanded poly tetrafluoroethylene), or permanent and nonreversible (e.g., liquid injectable silicone, polymethylmethacrylate).

Complications and adverse reactions can occur with all fillers and all filler procedures. The most common side effects include hematomas, ecchymoses, swelling, erythema, discoloration, visibility, or palpability of the filler. Hypersensitivity and tissue necrosis are rare and most distressing. Filler migration, granuloma formation, infection, and delayed inflammatory reactions do not usually occur with nonpermanent biodegradable fillers.

Hematoma and ecchymosis are due to extravasation of blood cells into the tissue due to needle injury of blood vessels. Alcohol consumption, blood thinners, NSAIDs, aspirin, vitamin E, omega 3, and probably other herbal agents facilitate the occurrence of hematoma. If these drugs are used prophylactically, proper discontinuation of their intake prior to the procedure, and refraining from alcohol consumption, may prevent some of the bleeding events. Firm pressure immediately after the injection and ice-pack application may minimize the bleeding, if it occurs. Historically, animal-derived collagen-based fillers (i.e., Zyderm and Evolence) were associated with less bleeding due to induction of platelet aggregation, but they are no longer commercially available.

Transient swelling and redness occur immediately after a filler injection and usually last a few hours to a few days. These phenomena are probably secondary to the inflammation induced by the product itself, injection trauma, and tissue manipulation by massaging or molding. Some products are more prone to induce tissue swelling due to their hygroscopic properties (e.g., hyaluronic acid-based products). In addition, certain facial areas, such as the lips, are particularly sensitive to injections and inevitably swell after the procedure. Prolonged icing of the area without direct contact between the ice cube and the skin can assist to diminish this phenomenon.

More prolonged swelling can signal overcorrection. Tear trough depression is especially sensitive to overcorrection. Permanent or periodic (usually in the mornings) swelling in this area may require dissolving the filler by enzyme hyaluronidase.^{22,23}

Visibility and palpability of the filler are often related to an improper injection technique. Although discoloration in the injection site can be induced by hemosiderin deposits following postprocedural hematoma, it is often due to superficial implantation of the filler in a way that the original color of the product or its interaction with the tissue shows. A bluish tint in the

areas where hyaluronic acid was implanted too superficially is known as the Tyndall effect.²⁴ This can also be successfully treated by hyaluronidase.^{22,23}

Palpable nodularities can be observed after improper injection of several fillers. Nodularities after Bellafill are observed as a result of uneven delivery of material due to clumping of the polymethylmethacrylate microspheres. Superficial implantation of Radiesse may create a visible whitish cord along the implantation route. To avoid this happening, an adequate practitioner's training is needed prior to the clinical work with the fillers. A physician has to adopt a proper technique of even delivery of these products to the area at the deep part of the dermis or at the dermal-subcutaneous junction. In most cases, immediate postprocedural vigorous molding of the tissue will diminish filler palpability.

The most serious complication after dermal filler implantation is vascular compromise that can lead to necrosis of the overlying skin or even blindness. The most common fillers to cause blindness were autologous fat (47.9%) and hyaluronic acid (23.5%).²⁵ Having a detailed knowledge of vascular anatomy prior to injecting is key to prevention of adverse outcomes. When injecting into the glabella, nasal region, nasolabial fold, or forehead, the most common sites for a complication of blindness, caution is necessary to avoid intravascular injection. Inject slowly in a retrograde fashion and with minimal pressure. Aspirate before injecting and use a small-diameter needle. Inject small quantities (i.e., less than 0.1 mL) to prevent large quantities from entering an artery.²⁵ Similarly, a higher rate of side effects was found with more tissue-traumatizing techniques, such as fanning, rapid injection rate, and higher volumes of the product.²⁶ The initial manifestations of intravascular injection leading to skin necrosis are immediate blanching and pain.^{27,28} Different treatment modalities have been suggested to treat imminent necrosis, such as massaging, warm compresses, nitroglycerin paste, and systemic steroids, but their efficacy is not well established.²⁹ Local wound care, after necrosis settles in, is of paramount importance to reduce the extent of scar formation.

Hypersensitivity reactions are the most distressing adverse effects occurring with soft-tissue augmentation. Every single filler material can cause this complication, but the risk rate differs among products. There are also patient-related factors that affect the incidence of the hypersensitivity. Allergic reactions to bovine collagen have been well described with Zyderm (Figure 34.1). The bovine collagen component of Bellafill may evoke the same type of reactions in sensitive individuals. Since introduction of a single skin pretest in the United States, the incidence of a localized hypersensitivity at the test sites has been published in three separate studies. In the Pivotal Trial, 0/128 patients or 0% had a positive skin test.³⁰ In the Acne Scar Study, 3/175 or 1.7% had a positive skin test.³¹ In the Five-Year Post Approval Study, 8/1211 or 0.66% had a positive skin test.³² These reactions resolve with time as the bovine collagen is resorbed by the host.

The rate of hypersensitivity reaction with most of the hyaluronic acid-based fillers is less than 1%. Between 2007 and 2015, global hypersensitivity to the Restylane fillers ranges from 0.001% to 0.002%.³³ Since 2000, the amount of protein in the raw product has decreased, and the incidence of hypersensitivity reactions has decreased. Fifty percent of these reactions are immediate and resolved within less than 3 weeks. The risk of strong but transient, delayed reaction is approximately 0.3%.^{34–37}



Figure 34.1 Zyderm OR-induced granulomatous reaction.

Whereas hypersensitivity reactions are self-limited with nonpermanent fillers, a completely different course is expected when such a granuloma develops with permanent and nonreversible products. With Bellafill, the rate of granuloma formation was 1.7% over 5 years in the study that had the specific purpose of determining the incidence of granulomas and overall safety (Figure 34.2). All granulomas responded to medical treatment, and only 0.9% of patients had an ongoing granuloma at the end of the study. These were diminished overall, but the patients were still being medically treated after the conclusion of the study.³²

The liquid injectable silicone, called dimethicone (dimethylpolysiloxane), has been used extensively for soft tissue augmentation for many years. Although considered biologically inert, this material has been reported as potentially inducing a granulomatous inflammatory response of variable severity often due to large-volume injection or adulterated material. A remarkable paucity of reports about the development of complications after injections of liquid silicone is probably related to its illegal or semilegal use in most countries.³⁸ When using silicone in a microdroplet technique for lip enhancement, the incidence of granuloma formation is estimated to be approximately 2%.³⁹

Nonreabsorbable gel polymers (Bio-Alkamid, Aquamid) are approved for use in Europe but have not been released by the FDA. Those products may induce severe inflammatory and/or infectious granulomatous reactions at any point from the

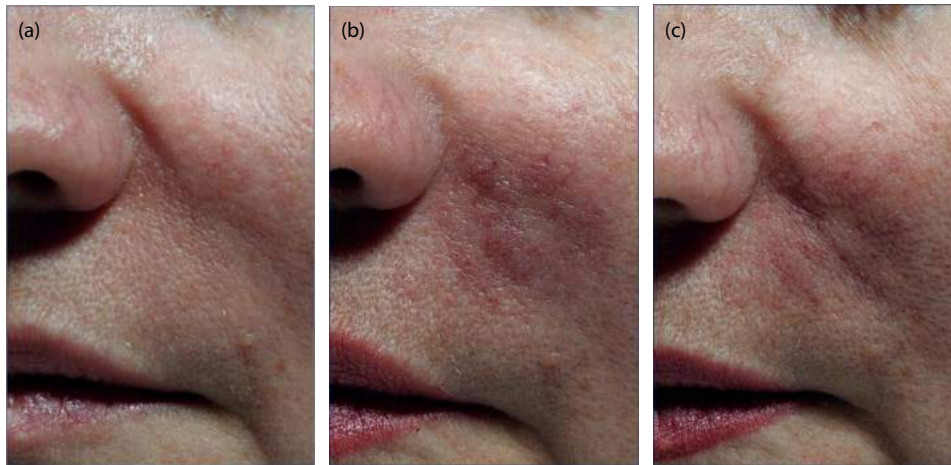


Figure 34.2 (a) The nasolabial fold 3 months after Bellafill injection, (b) granuloma formation (pictured 3 years and 6 months after initial injection), and (c) resolution of granuloma after 2 weeks of treatment. (Courtesy of Suneva Medical and permission of Cohen S et al. *Dermatol Surg* 2015;41:S302–S313.)



Figure 34.3 Bio-Alkamid OR-induced delayed inflammation.

implantation time. In some cases, treatment of these adverse effects is extremely difficult (Figure 34.3).^{40–43}

Botulinum Toxin A

Botulinum toxin A (BTXA) has become a widely used drug in cosmetic dermatology. There are currently three forms of BTXA commercially available that share FDA-approved indications for treating glabellar lines and cervical dystonia: onabotulinumtoxin A (Botox/Vistabel), abobotulinumtoxin A (Dysport/Azzalure), and incobotulinumtoxin A

(Xeomin/Bocouture). Botox and Xeomin are also approved to treat blepharospasm. Botox is uniquely approved for axillary hyperhidrosis, upper limb spasticity, chronic migraine headaches, urinary incontinence due to detrusor overactivity, and lateral canthal lines. The spectrum of possible adverse effects of BTXA is broad, but the effects are generally mild and transient. The major tools for preventing adverse effects from BTXA are knowledge and skill. Knowledge of the facial and extrafacial muscles allows physicians to select the optimal dose, time, and technique for injection. The most common adverse effects of BTXA injections are pain, hematoma, flu-like syndrome, headaches, focal facial paralysis, and muscle weakness.^{44,45} Severe side effects with cosmetic use of BTXA are rare and related to extreme overdosing or illegal use of an unapproved toxin.^{46–48}

The majority of BTXA-associated adverse reactions remain to be local and transient. In the glabellar area, the most important potential side effects used to be blepharoptosis and diplopia, reaching approximately 5% in the early period of BTXA use. With better understanding of glabellar complex muscle function and a more precise dosing, this adverse effect has become extremely rare.⁴⁹ If it occurs, Iopidine ophthalmic solution 0.5% is useful until the ptosis resolves.

While treating the forehead wrinkles, eyebrow ptosis and asymmetry are the major potential side effects.⁵⁰ A thorough analysis of the face animation is crucial to avoid injecting patients whose forehead wrinkles are related to the use of frontalis muscle to keep visual acuity (Figure 34.4). In most cases, coinjection of the forehead depressors (glabellar complex) minimizes the risk of brow ptosis. Careful planning of injection doses and sites will decrease the risk of eyebrow position asymmetry. If it happens, additional injection of the less deactivated muscle will correct it.

In the periorbital region, partial lip ptosis resulting from weakening of the zygomaticus major muscle is the most devastating complication, because it affects smile symmetry (Figure 34.5).⁵¹

To avoid this happening, no toxin should be injected behind the zygomatic bone. BTXA can be used in the lower



Figure 34.4 Brow ptosis due to inadequate injection of botulinum toxin A to forehead (a) before injection and (b) after injection.



Figure 34.5 Labial ptosis due to paresis of the left zygomaticus muscle by periorbital botulinum toxin A injection.

eyelid to improve wrinkles and widen the eye. In these cases, minute doses of the toxin are recommended, because higher doses induce lower eyelid edema and incomplete sphincter function of the eyelids.⁵² Although BTXA for lateral canthal rhytids usually does not suppress tear production, dry eye is a possible complication of this procedure. Treatment of dry eye and exposure keratitis is symptomatic and includes lubrication.⁵³ Another rare complication reported recently after BTXA injection in the lateral canthal area is proptosis associated with thyroid disease. Although proptosis represents progression of the patient's preexisting thyroid eye disease, cosmetic use of BTXA unmasks it.⁵⁴

Procedures for the lower third of the face require a higher level of expertise, because all the muscles there have specific functions. Different muscles in this zone interdigitate with others and, in some cases, act as antagonists. Thus, this region requires a rigorous evaluation by the physician, with precise diagnosis and technique of BTXA application. Platysmal bands can be temporarily improved by BTXA with redundant skin being a limiting factor of this treatment success. Dysphagia and airway obstruction are the potential side effects related to the toxin dosing and diffusion.⁵⁵

Hyperhidrosis refers to the medical condition of excessive and uncontrollable sweating. There are two types of hyperhidrosis: primary focal and secondary generalized hyperhidrosis. Primary focal hyperhidrosis refers to excessive sweating that is *not* caused by another medical condition, *nor* is it a side effect of medications. The excessive sweating is the medical condition itself and usually begins in childhood or adolescence. This type of sweating occurs on very specific areas of the body (described as *focal* areas) and is usually relatively "symmetric" (i.e., axillae, hands, feet, face, or head). Secondary generalized hyperhidrosis is caused by another medical condition or is a side effect of a medication. Unlike primary focal hyperhidrosis, people with secondary hyperhidrosis experience sweating on larger areas of the body, even during sleep, and it usually begins in adulthood.

A broad spectrum of treatment modalities are available to treat primary focal hyperhidrosis, including topical antiperspirants containing aluminum chloride, iontophoresis, Botox injections, miraDry, lasers, oral anticholinergic agents, and surgery. Chemodenervation, using botulinum toxin, is a safe and effective treatment for primary focal hyperhidrosis of the axillae, palms and soles, and face and head. Fifty percent of patients report that after one treatment they are free of excessive sweating for more than 7 months in the axillae, and more than one third of patients are still free of excessive sweating after 1 year. This treatment is highly effective with a paucity of side effects. Fine motor impairment after palmar injection of BTXA has been rarely reported.⁵⁶

Chemical Peels

Chemical peeling is a procedure used for cosmetic improvement of skin or for treatment of some skin disorders. A chemical exfoliating agent is applied to the skin to destroy portions of epidermis and/or dermis with subsequent regeneration and rejuvenation of the tissues. Chemical peels are divided into three categories, depending on the depth of the wound created by the peel. Superficial peels penetrate the epidermis only, medium depth peels damage the entire epidermis and papillary dermis, and deep peels create a wound to the level of the midreticular dermis.

The list of potential complications of chemical peels includes pigmentary changes, infections, milia, acneiform eruption, scarring, and cardiotoxicity.

Reactive hyperpigmentation can occur after any depth of chemical peels (Figure 34.6). Usually lighter complected patients have a lower risk for hyperpigmentation, but genetic factors play an important role, and sometimes light patients with "dark genes" hyperpigment unexpectedly. Skin priming using a combination of hydroquinone and tretinoin cream (Kligman formula) before the superficial and medium depth peels and early introduction of this preparation after deep peels reduces the rate of this complication. Demarcation lines can be avoided if the boundaries of the peeling area are hidden under the mandibular line and feathered gradually to the normal skin. Hypopigmentation after phenol peels is proportional to the depth of the peel, amount of the solution used, number of drops of croton oil in the solution, inherent skin color, and postpeel sun-related behavior. Intradermal nevi can hyperpigment after deep peels.

Bacterial and fungal complications in chemical peels are rare. Patients with a positive history of herpes simplex infection are treated prophylactically with acyclovir or valacyclovir



Figure 34.6 Reactive hyperpigmentation after deep chemical peel in a dark-skin patient (a) before, (b) 3 weeks after the peel, and (c) 4 weeks after introduction of a topical bleaching preparation.



Figure 34.7 Disseminated herpes simplex infection in a patient after chemical peel.

during medium and deep peels until full reepithelialization is achieved (Figure 34.7). Toxic shock syndrome has been reported after chemical peels.⁵⁷

Milia or epidermal cysts appear in up to 20% of patients after chemical peels, usually 8–16 weeks after the procedure (Figure 34.8). Electrosurgery is simple and effective to treat this postpeel complication.

Acneiform eruption after chemical peels is not rare and usually appears immediately after reepithelialization. Its etiology is multifactorial and is either related to exacerbation of previously existing acne or is due to overgreasing of newly formed skin. Short-term systemic antibiotics, together with discontinuation of any oily preparations, will usually provide satisfactory results.

Scarring remains the most dreadful complication of chemical peels. The contributing factors are not well understood. The most common location of such scars is in the lower part of the face, probably due to more aggressive treatment in



Figure 34.8 Postpeel milia.

this area or to the greater tissue movement, due to eating and speaking, during the healing process. Delayed healing and persistent redness are important alarming signs for forthcoming scarring. Topical antibiotics and potent steroid preparations should be introduced as soon as this diagnosis is made.

The most important potential complication exclusive to phenol-based peels is cardiotoxicity. Phenol is directly toxic to the myocardium. Studies in rats have shown a decrease in myocardial contraction and in electrical activity following systemic exposure to phenol.⁵⁸ Because fatal doses ranged

widely in these studies, it seems that individual sensitivity of the myocardium to this chemical exists. In humans, sex, age, previous cardiac history, and blood phenol levels are not accurate predictors for cardiac arrhythmia susceptibility.⁵⁹ Cardiac arrhythmias in less than 30 minutes have been recorded in up to 23% of patients, when full face peel was performed.⁶⁰ Adequate patient management reduces this complication to less than 7%.⁶¹ No hepatorenal or central nervous system toxicities have been reported in the literature with properly performed chemical peels.

CONCLUSIONS

Each one of the procedures in dermatology carries a risk of potential complications. They can be mild and reversible or severe and permanent. Most of them are avoidable and treatable.

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Life-threatening dermatoses in travelers

Larry E. Millikan

Severe skin reactions/conditions are of particular concern when the traveler is away from home, and medical care is unfamiliar or of uncertain caliber. Perhaps the most significant of these conditions is Stevens–Johnson syndrome, which may occur after the use of antimalarials such as Fansidar for prophylaxis while traveling in Africa. Travel remains a rapidly growing enterprise with more remote destinations appearing on the radar screen each year, making the previous review a basis for this update.¹

More commonly, a serious dermatosis begins before the trip, progresses, and becomes significant while the traveler is away from usual medical care, not following his or her usual dietary and health habits, and often has a difficult time finding and/or communicating with medical personnel. Older patients (often the usual travelers with both time and means) have particular challenges—daunting lists of drugs and potential interactions, as well as the possibility of new drugs (and side effects) beginning around the time of the travel. The pediatric population is part of this new trend, and the smaller patients have a higher risk for both toxic (venoms) and drug reactions.¹ The occasional traveler rarely keeps important medical documents with him or her, but they are necessary during an acute/life-threatening event, as the following example demonstrates.

CASE REPORT

A male tourist in his 50s is brought to the emergency room from the French Quarter in New Orleans, having been found confused, weak, tremulous, and unable to walk with a steady gait. He is placed in an emergency cubicle, where he is found to be hypertensive with a temperature of 38.5°C. As history taking commences, he becomes incoherent and lapses into a coma. Examination reveals moderate obesity, hypertension, and spreading waxy urticarial plaques (Figure 35.1) over most of his trunk.

He responds to pain and pressure with withdrawal, but otherwise he is unresponsive to verbal commands and questions. Preliminary laboratory studies reveal glycosuria, hyperglycemia, polymorphonuclear leukocytosis, and elevated erythrocyte sedimentation rate and C-reactive protein. Examination of the protuberant abdomen shows slight organomegaly of the liver and possibly the spleen, but there is minimal ascites. To obtain more information, the patient's wallet is examined, and of interest are the addresses of the two premier oyster houses in the New Orleans French Quarter. With this information and little else of medical history—plus signs of hypotension, fever, and sepsis—the dermatologic consultants suggest the likelihood of infection from *Vibrio vulnificus* due to oysters. Intravenous ciprofloxacin is started approximately 3

hours after arrival at the hospital, when all of the preliminary data and consultations had been collated. Six hours later, after an up- and-down course during the night, the patient expires without ever regaining consciousness. On autopsy, *V. vulnificus* is confirmed with a septic vasculitis and advanced liver and kidney disease, as well as advanced coronary disease—all typical for the usual patient with life-threatening and usually fatal *Vibrio* sepsis.² More recently, Hurricane Katrina prompted other travel on the part of rebuilders of the Gulf Coast and at the same time resulted in a resurgence of the *Vibrio* problem.^{3,4}

These types of events might have different outcomes, if medical histories are made available when patients present to a major hospital in North America or Europe. Much more tenuous events can transpire in remote sites for ecotourism and in marginal medical facilities in so many developing countries.

Infectious Dermatoses

Infectious dermatoses are the first and most serious risk for the traveler, especially for one partaking of the exotic “out of the way” trips becoming in vogue as well as the popular ecotourism ventures, which as a routine are far from the fringes of civilization.

Food-Borne Infections

The case report underscores serious dermatologic conditions from food-borne infectious agents. Although it is more common to have the famous gastrointestinal (GI) sequelae—Montezuma's revenge, Tut's curse, and Delhi Belly are common descriptors—the primary challenge with these food-borne GI reactions is to restore fluid balance, which is difficult to accomplish in some patients without hospitalization. Very young or infirm patients can be at mortal risk, unless proper support is available. Of greater concern is the increase of contamination of the food chain in modern countries with various pathogenic agents, such as *Escherichia coli*, with widespread exposure in various fast food establishments, where the usual assumption is safety, and therefore caution is at a lower level. These same persons are ordinarily more careful while traveling, but as this evolves, concern that such adulteration of foodstuffs (as seen in animal foods in which potential toxic “expanders” were resulting in many pet deaths from renal failure) perhaps equals infection as a major concern.

It is reminiscent of the “porphyria Turcica”⁵ from the ingestion of seed grains containing toxic antifungal powders—marked “not for ingestion” (in English), unintelligible to the rural people who desperately needed food and assumed that the grains were safe for cooking.² In the treatment phase, cutaneous sequelae may be an additional reason for the hospitalization—a result of reaction to the drugs

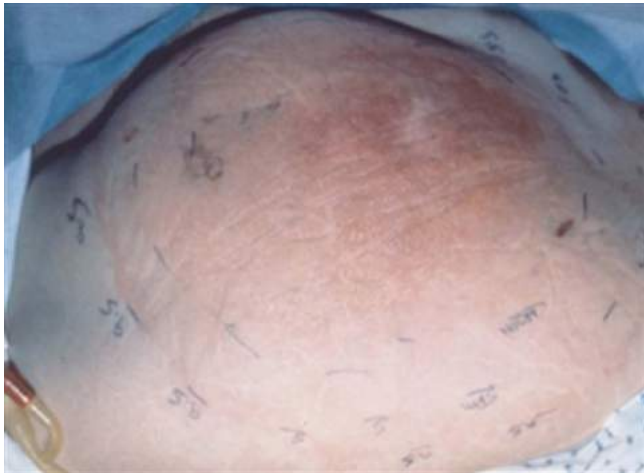


Figure 35.1 Enlarging waxy plaques of *Vibrio vulnificus*.



Figure 35.2 Severe bullous erythema multiforme.

prescribed (erythematous [EM] vide infra; Figure 35.2), sudden systemic collapse and sepsis complications, such as vasculitis (Figure 35.3) and mechanobullous eruptions. These results are usually indicative of multiorgan involvement and potential organ failure and death. Cholera and typhoid fever are always risks to travelers, whether in the “first world” or “third world,” because global sources of foods compromise the safety of the food chain, even in Europe and the Americas. An “ecotourist” may take all the right precautions in the country, only to become seriously ill on the way home!

ENVIRONMENTAL SOURCES

Traveling away from cities and civilization exposes one to many native infections and infestations that can be serious to those who are not natives and lack acquired immunity. Particularly susceptible are older patients, persons with immune deficiencies from pharmacotherapy (transplants, certain chemotherapy, etc.), and persons with infectious



Figure 35.3 Petechial lesions of drug vasculitis.

immunodeficiencies. The cutaneous presentations of these include petechiae (*Rickettsia*, *Meningococcus*, and some gram-negatives—palpable purpura, ecthyma gangrenosum, and ulcers, such as those seen in *Mycobacterium ulcerans* infections) (Table 35.1).¹

This caveat is important: In an abnormal host, classic presentations seldom occur and diagnosis in atypical presentations requires a high index of suspicion and compulsive use of all diagnostic tests to provide confirmation of diagnosis. Many of these conditions require early aggressive treatment to ensure survival. Rickettsioses, as an example, respond best with early systemic therapy; late therapy is associated with a much lower survival rate.³

CASE REPORT

The patient is a 24-year-old former Peace Corps worker seen due to recurring problems in his amputee stump. He was working in Africa in the 1960s during a time of increased greenery due to a wet phase in the weather. It was assumed that the initial event was trauma to the left leg from the sharp margins of the

Table 35.1 Petechial/Purpuric Presentations

Rickettsia
Meningococcemia
Henoch–Schönlein purpura
Morbilliform
Rubella
Morbilla
Other viruses
Staphylococcal scalded skin syndrome
Many of the herpes viruses ^{1–9}
Drug eruptions

local grasses. The infection proceeded to an ulcer unresponsive to therapy: Thus began a scenario of repeated debridement, grafting, and recurrence—then ultimately amputation, below the knee, then above the knee, then at the hip. On examination, he appeared normal for his age except for his left lower quarter, where there were several EM and granulomatous arcuate lesions surrounding the scar from the last hip procedure. Biopsy of these granulomatous areas revealed heavy cellular infiltrate that was nearly magenta on the acid-fast stain, being loaded with organisms. Further surgery and trials of new antimicrobials were started.

Many of the atypical acid-fast organisms also are found on vegetation where they come in contact with animals. Many infections remain a challenge for chemotherapy. Although the effectiveness of clarithromycin has been documented, it usually needs some surgical assistance for the best results. This concerns life-threatening conditions; the prolonged course is debilitating to the patient—the only respite being the cryophilic nature of *M. ulcerans*, which does limit its spread to the body's core while the host remains in good health. Much later, it has become apparent, concerning the extensive deforming spread of *Mycobacterium chelonae* and *Mycobacterium avium intracellulare*, that it begins to impinge on vital structures—thus a threat to life in addition to limb.

So the traveler can acquire infectious organisms that slowly destroy life as well as have much more acute episodes with infectious vasculitis, sepsis, and a stay in the intensive care unit (ICU). Some of these organisms are from vegetation, and others are from arthropods—*Plasmodia*, *Rickettsia*, and many others.³

Malaria remains a risk in much of the developing world, although the newer insecticidal curtains have been helpful in

limiting the spread after the great increase without dichlorodiphenyl-trichloroethane (DDT) use. Cutaneous sequelae are less frequent. Usually, the patient in good health will usually survive and clear with appropriate treatment. Much more of a risk are the potential reactions to antimalarial prophylaxis. These have been documented—erythema multiforme, agranulocytosis with subsequent sepsis, and the dapsone/DRESS syndrome (Figure 35.4). All of these outcomes have become serious, if not treated early, intensively, and usually with hospitalization. The seriousness is compounded by the fact that the patient on malaria prophylaxis is usually far from medical care.

The most serious of infections are those of the filovirus group. They present with impressive cutaneous hemorrhagic findings, associated with a high mortality from, for example, the Marburg and Ebola viruses.³ While previously exposure was limited, the epidemic in West Africa 2013–2015 was a true epidemiologic crisis spreading from Africa to Europe and North America with travelers—both tourists and health-care workers. Hospitalization, isolation, and intensive care with precautions for the health-care team (due to the high mortality and infectivity potential) are needed. Therapy is still on a case-by-case basis due to the lack of definitive antiviral therapy. Immune serum is playing a role in enhancing survival, as an increasing number of survivors, mostly health-care workers, are providing this life-saving option. Still, support therapy is the usual approach, maintaining essential organ function until the patient recovers.⁸

The usual bacterial and rickettsial infections also need to be considered for patients ill with petechial and/or morbilliform exanthems. The differential diagnoses need always to be reviewed to be sure that the diagnosis is not missed (Table 35.1).



Figure 35.4 Multiple pustules—*Solenopsis*/fire ant.

It is critical to establish the diagnosis and treat expectantly to be certain that the patient survives. Many of these infections respond only with early therapy. Early aggressive diagnosis and therapy are key!^{18,9}

Allergic/Immunologic Reactions

Immediate/Immunoglobulin-Mediated Type I

Anaphylactic/Immunoglobulin E

Anaphylaxis is the most significant of disorders affecting travelers and may result in death in a very short span of time. It may also be so sudden that more sophisticated medical facilities are not close enough to be able to offer their life-saving expertise. Patients who know of their risk are often prepared for emergencies with injectables, such as epinephrine carried with the person. This type of reaction (usually immunoglobulin E [IgE] mediated) can result from reexposure to antigens, such as insect venom, drugs, or even contact antigens (usually environmental but can be due to personal care products including creams, sunscreens, and lotions). Initial presentation may be that of angioedema.^{2,10,11}

When anaphylaxis occurs, the events are too rapid in sequence for dermatitis to appear, but the usual previous antigenic exposure is either urticarial or EM in nature. The patient's physician should alert the future traveler to reexposure risk and recommend prophylaxis, such as antihistamines or epinephrine/antihistamine injection kits. Whereas the patient may be aware of the agent (arthropod, etc.) in the home environment, there may be related causes/agents encountered while traveling that are unfamiliar. It is important that the physician make an effort to educate the patient to these new threats (in other words, the different species of *Vespa*, *Apis*, *Latrodectus*, *Solenopsis*, etc. [Figure 35.4], the botflies, and other groups). This education can be lifesaving in the case of bee/hornet/wasp allergies. Avoidance is often far better than the prevention of anaphylaxis after exposure.¹²

Whereas airborne arthropods are the main cause for these venom reactions, there are others found at the seaside that vary from minor localized reactions to widespread skin involvement, predisposing to serious (and occasionally life-threatening) skin infections. Coelenterates are perhaps the most significant in this category, and they can be ubiquitous and a serious health problem on the shores of Australia, where emergency care is available at the beach to neutralize the toxins and to avoid a trip to the hospital. Far more dramatic are the larger animals—sea snakes, giant clams (Figure 35.5), moray eels, barracuda, sharks, and various rays (such as the one that killed the zoologist Steve Irwin)—but it should be emphasized that these are extremely rare, and the morbidity is from trauma or venoms (not anaphylactic in nature). Most exposures at the beach—sea bathers eruption, swimmers itch, creeping eruption, and so forth—are sources of minimal morbidity unless large areas of skin are involved or an unusual allergic reaction occurs.

Type 2 or 3

Type 2 (vasculitis and the immuno-/mechanobullous dermatoses) and 3 (immune complex reactions) are rare in environmental exposure but hypothetically can occur after hypersensitivity to various venoms, such as solenopsis⁴ and subsequent exposure with possible intravascular dissemination of the venom with extensive immune complex formation and cascades of inflammatory mediators. These types can cause acute organ



Figure 35.5 Giant clam at the Great Barrier Reef.

failure (liver, kidney) and a picture not unlike infectious sepsis. These are rare and, in extreme cases, result in ICU stays.

Delayed/Cell Mediated

Type 4

Delayed reactions can be just as serious as immediate reactions under the proper circumstances. Whereas atopic dermatitis is generally considered to be related to IgE, atopic patients seem to develop type 4 reactions to plants in increasing amounts as they age. The timing may be the significant factor. Many travelers have a vacation ruined by widespread rhus contact dermatitis; the patient, even under the best of care, cannot enjoy the destination city and its charms. Without proper care, and in certain climates, the heat and humidity can lead to secondary infection, and the end result can approach the morbidity of a second-degree burn or worse. There are well-documented cases of nephrogenic streptococcus, resulting in acute renal complications, hospitalization, and rarely dialysis.

When the exposure takes place during the trip, the rapidity of the reaction often relates to the degree of sensitivity and the breadth of exposure. In many cases, the source is a related species unfamiliar to the traveler. The possibilities are immense. The main plant groups are *Primula* (mostly in the United Kingdom), *Compositae* (worldwide), *Alstroemeria* (largely acquired in the floral trades), *Rhus* (United States), *Allium*, and certain legumes that can be a source of allergy, largely manifested by food allergy, but occasionally cause type 1 and type 4 reactions. Many of these patients present with occasional urticaria or dermographism (Figure 35.6).

With a high degree of sensitivity, widespread vesiculobullous lesions increase the risk of infection and sepsis requiring hospitalization. The treatment varies with the infecting organism, but parenteral antimicrobials are the main indication for hospitalization and are the most rapid means for quick recovery.

CONCLUSIONS

The current most significant trend in travel is “ecotourism,” which places the traveler directly in the environment and often

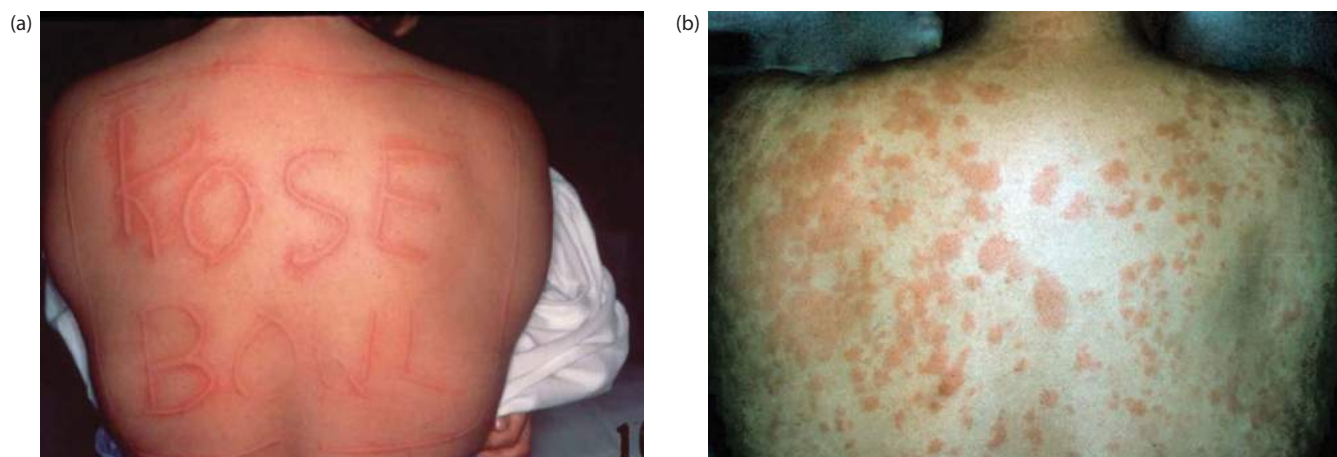


Figure 35.6 (a) Dermatographism seen in (b) type 1 allergy.

in remote areas that make rapid response to severe and potentially life-threatening reactions a big challenge. Additionally, the apparent increasing number of disasters with following influx of relief workers has expanded the numbers of patients at risk.

Travel is now more accessible to patients with significant morbidities such as diabetes, immunosuppression in transplant patients, and even advanced malignancies under chemotherapy. Minor environmental dermatoses and infections easily addressed at home can drastically evolve to threaten life, when one is away from the usual medical support system. Evacuation and inherent delays in transfer can allow a minor and local condition to spread, impetiginize, and possibly secondarily involve internal organs, mandating hospitalization. Dermatoses that respond to simple local measures normally become life threatening when care is delayed or complicated by measures in evacuation. The prepared traveler should have significant medical information available, especially when morbidities, such as diabetes or other metabolic conditions, predispose the traveler to greater risk and complicate usual recovery. Similarly, patients with a long list of medications need to have documentation of it, as well as an understanding of potential risks such as photosensitivity. Most major medical institutions now have travel medicine units that should be the first stop after the trip is finalized. This consultation educates the traveler as to risks and the necessary preparations, vaccinations, and prophylactic drugs, as well as prepares him or her for environmental exposures.

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Information management

Michelle Xu, Yusuf Anwar, and Daniel Mark Siegel

Contemporary medical practice is saturated with what data scientists call “information overload.” Consider that “90% of data in the world today has been created in the last two years alone.”¹ Digesting the enormous amount of available data efficiently and effectively in the midst of clinical emergencies can become problematic were it not for the rapid advance of technology.

Amid the smartphone revolution, a number of digital portable applications have been developed that provide a wealth of resources. This chapter provides an overview of the various “apps” and resources available to either iPhone and/or Android users. It has been divided into three sections: General Dermatology, Emergency Dermatology, and General Medicine.

GENERAL DERMATOLOGY

Decision support system (DSS) software processes signs, symptoms, and relevant laboratory findings, ultimately helping the user to make diagnoses and decisions on possible treatments. DSS is commonly used for hypertension and diabetes among other medical ailments; however, there are programs related to dermatology. A key one, devised by two dermatologists, Papier and Goldsmith, is *VisualDx* (<http://www.visualdx.com>), which provides access to over “10,000 peer reviewed images” that cover a wide variety of cutaneous manifestations. A benchmark of 100 million views has been reached.² The physician is able to search VisualDx’s vast database by entering signs and symptoms, visual patterns, diagnosis, medications, and other available information. This then provides access to high-resolution images to guide diagnosis and treatment.

There are three major components to VisualDx:

- *Differential Builder* allows the user to choose a clinical situation. Patient symptoms and signs are then selected to build a relevant differential diagnosis. There is a Quick Start function that assists the user in selecting pertinent patient factors to narrow down the differential diagnosis (see Figure 36.1).
- *Diagnosis Search* function shows each diagnosis with an associated differential diagnosis list and links to a separate description of each entity. The subsequent entry contains diagnostic criteria, relevant medications, and the appropriate ICD coding scheme.
- *Medication Adverse Events* provides images of cutaneous manifestations of adverse chemical reactions. Relevant literary citations, as well as treatment guidelines, are provided.

Teledermatology is a useful way to provide services remotely. There are many applications available, and some of the more interesting ones will be discussed.

Klara (<https://www.klara.com>) is a teledermatology application that allows physicians to communicate with their patients remotely. Patients are able to send images of their cutaneous conditions to their physicians. The images are accompanied by answers to a brief questionnaire developed by board-certified dermatologists. The dermatologists then use this application to find an appropriate diagnosis and corresponding treatment.³

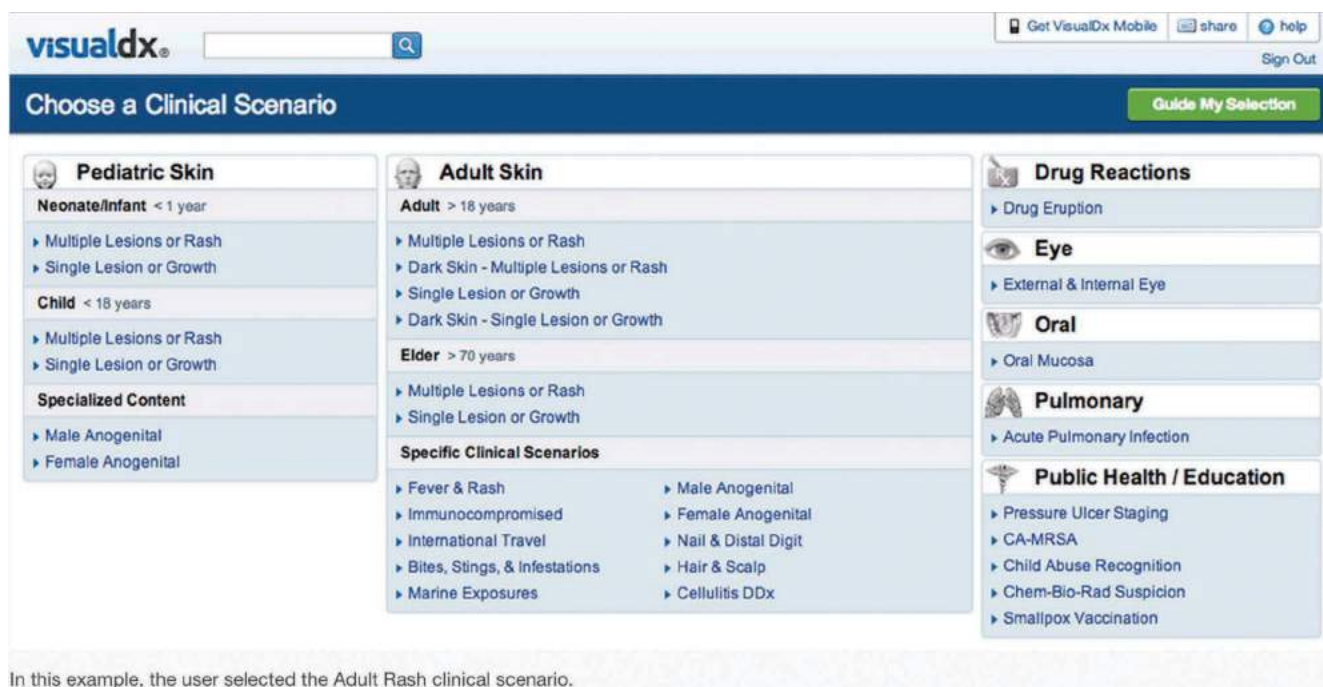
AccessDerm (<https://accessderm.aad.org>) is a program produced by the American Academy of Dermatology. It facilitates teledermatology for underserved patients in the same state as the provider. Given its strong design and functionality, it is likely that this program will have commercial use at some point in the near future.

UMSkinCheck (<http://www.uofmhealth.org/patient%20and%20visitor%20guide/my-skin-check-app>) is a unique application (iPhone only) designed by physicians associated with the University of Michigan. It is a fully featured program, designed to aid patients in self-examining potentially cancerous lesions, including the all-inclusive term, “moles.” Patients learn how to accomplish full-body checkups and are encouraged to track their lesions over time. The program reminds patients to check their lesions periodically and helps them create a database containing images taken over time. Additionally, there is a wide range of reading material and associated videos for the patient’s benefit; nonetheless, patients can use all of these resources and still need physician assistance.⁴

Derm Grand Rounds (<https://dermgrandrounds.com>) incorporates “crowd intelligence.” Patients submit images of their cutaneous manifestations to a panel of practicing physicians, residents, and other health-care professionals who analyze the image. The top two competing diagnoses are returned to the user.⁵

The concept of “crowd intelligence” arose when *CrowdMed*, a startup in California, attempted to use “crowd-sourcing.” The startup argues that the “collective wisdom” of a party of strangers has been used effectively in “finding missing persons, tracking down terrorists and picking stocks.” The argument is used to extend such a concept to diagnoses of medical conditions. “Detectives” registered with the application include physicians, residents, and the general public. Points are awarded for correct diagnoses.⁶

Dermatology A to Z (<https://www.aad.org/dermatology-a-to-z>) is the American Academy of Dermatology’s (AAD) comprehensive dermatologic database. The Android and Apple app provides a searchable index for various skin manifestations, a “Find a Dermatologist” directory searchable by name or location, and a real-time UV levels index. This “starter” app allows access to easy-to-read information on a number of dermatologic manifestations. There are answers to frequently asked questions (FAQs) about dermatologic conditions. The latter two



In this example, the user selected the Adult Rash clinical scenario.

Figure 36.1 VisualDX Differential Builder (<https://www.visualdx.com/video-tutorials/mobile-tutorial-differential-builder-ios>). (With permission from Visual DX.)

features use GPS locators to find relevant health-care providers and UV levels. Additionally, users have access to a monthly newsletter.

DermNet NZ (<http://www.dermnetnz.org>) is a free Web-based authoritative resource for patients and physicians. Its many illustrated pages are best known as a guide for management and treatment. Dermatologists and medical writers edit the content.⁷

DoctorDerm (<http://www.aocd.org/?page=doctorderm>) is designed to assist the lay public in understanding dermatologic diseases, terminology, and treatment. It is largely available offline, and it features GPS capabilities to help in locating nearby dermatologists. It is a free service provided by the American Osteopathic College of Dermatology.

PubMed On Tap (<http://www.referencesontap.com>) is an iOS-based mobile application for searching PubMed and PubMed Central to locate relevant publications. References can then be viewed or imported into reference applications such as EndNote.⁸

EMERGENCY DERMATOLOGY

Radiation exposure due to clinical examinations has increased nearly 600% from 1980 to 2006. With the Fukushima Daiichi scare in 2011 in Japan, accessing critical information in such scenarios has become increasingly important.⁹

Radiation Map (<https://itunes.apple.com/us/app/radiation-map-tracker-lets/id427091720?mt=8>) provides numerous data points of current radiation level and one's risk level. It provides official statistics about radiation exposure, based on local and national server data.

Pocket Geiger Counter Pro (<http://www.radiation-watch.org/2011/06/smart-survey-meter-will-be-available-in.html>)

by Radiation-Watch, is a premium service originally designed to provide access to a smart radiation detector in and around Fukushima Daiichi. The iPhone serves as a viewer when hooked up to a detector of beta and gamma radiation. The external detector has eight photodiode sensors that are used to detect radiation. Aluminum foil is used to screen out the alpha and beta particles.¹⁰

Premium features include oscilloscope access, recordings of date, time, and position of radiation detection, as well as visualization of the detection log. Additional peripheral devices allow the power source to be drawn from the iPhone itself, eliminating the need for batteries. The user's data are uploaded to a server, where it is combined with the data from over 10,000 users.¹⁰

Nuclear Plant (NP) Finder (<https://itunes.apple.com/us/app/nuclear-plant-finder-np-finder/id426851696?mt=8>) uses GPS to calculate the distance to nearby nuclear power plants, while mapping them on the screen of a mobile device. Clicking on the located plants on the map will open a window and provide external references about the specifications of the nearby plant (owner, technical details, operating time of the plant). This application currently contains data for a number of largely developed nations globally.

iTriage (<https://www.itriagehealth.com>) was created by two emergency medicine physicians. Its content was reviewed, according to their website (<https://about.itriagehealth.com/company-info/medical-content/>) by Harvard Medical School and provides a centralized and individualized health-care hub. *Doctor Search* allows a search for physicians near one's residence or current location easily and efficiently. It provides information regarding nearby health-care facilities, ranging from emergency rooms and urgent care centers to imaging

centers, mental health clinics, and pharmacies. *Symptom to Provider* allows one to work from symptoms to a possible differential and then access a list of physicians nearby who could treat these conditions effectively. Additionally, one can search for average wait times for nearby emergency rooms and urgent care centers. While en route to one's destination, there is the option to check into these centers via a mobile device. Last, one can view his or her personal health record (PHR) that is stored within Microsoft's HealthVault service.

GENERAL MEDICINE

Artnatomia (<http://www.artnatomia.net>) is an online tool that allows one to delve into the anatomic and biomechanic etiologies of certain facial expressions. Upon use of the application, one begins with level 1. This is a blank canvas (skull), where one can subsequently "slide" various layers of muscle onto the face. One can access further details on the etymology, shape, actions, and expressions of each muscle. Level 2 allows the user to select various actions for each muscle and view them visually on a beautifully rendered human face. For instance, if the user selects orbicularis oculi, he or she can see how the muscle plays a role in compression and elevation of the eyelids via real-time movements.¹¹

Medscape (<http://www.medscape.com>) offers access to one of the most comprehensive medical databases available. It offers up-to-date information on a wide range of medical conditions. Medical content ranges from reviews and patient educational material to expert columns and book reviews. Medscape has partnered with WebMD to offer an expansive list of resources. This includes reviews and syntheses of major medical conferences, access to over 100 medical journals and textbooks, as well as access to *MedPulse*, a weekly newsletter with information relevant to one's specialty.

Epocrates (<http://www.epocrates.com>) is currently the most frequently used medical reference application available

about many agents. The database for Epocrates has been established with the help of the *British Medical Journal* (<http://best-practice.bmj.com>), permitting access to current information from the *BMJ Best Practice*.¹²

Epocrates Bugs and Drugs (<http://www.epocrates.com/e/BugsAndDrugs>) is an app that gives GPS-derived information about bacterial sensitivity in a chosen area for making informed decisions about therapy. This free app should not be mistaken for *Bugs & Drugs*, a product of Alberta Health Services, which is a comprehensive application for Android and Apple mobile devices. It serves health-care professionals regarding antimicrobials, their indications, and optimal use for treatment of infectious diseases.

Canopy Translator (<http://www.canopyapps.com>) features three products that comprise a comprehensive medical translation application:

- Canopy Medical Translator (see Figure 36.2) provides commonly used phrases, live medical interpreters, and "visual translations." The latter allows patients to both see and hear the translation of a specific phrase selected in their native language.
- Canopy Medical Spanish provides self-paced instruction at varying levels of difficulty that feature custom videos.
- Canopy provides National Certification for Bilingual Healthcare Providers. This examination provides recognized certification for the ability to work with patients in multiple languages. This certification allows health-care institutions to maximize the skills of their staff by stratifying varying levels of competency.¹³

HealthMap (<http://www.healthmap.org>) was founded by Children's Hospital in Boston in 2006, providing real-time information about disease outbreaks. Alerts can be set to notify the user when an outbreak reaches his or her area of residence. The first person to spot an outbreak in a given area receives



Figure 36.2 Canopy Translator (<http://try.canopyapps.com/canopy-medical-translator-app/>). (With permission from Canopy.)

recognition on the HealthMap webpage along with credit as a “disease detective.”

One of the recurring themes in the digital age is concern about garnering access to reliable and verifiable data. Many digital applications make claims about achieving a goal that some may find suspect. An example is the proliferation of ultrasound mosquito repellants in the past few years. Recently, a prestigious advertising award went to a radio station based in Brazil. The station claimed that their 15 kHz tone, when broadcast over air, would repel mosquitos. A tremendous amount of media coverage was given to the grand claims. No more lotions, smokes, or “rolled up newspapers” were needed. Users could sit outside and relax, while their radio would emit signals to protect them. A number of review studies backed by scientists in the community have repudiated the veracity of these claims.

CONCLUSIONS

Amid the advent of overwhelming groves of information, a number of viable technologic solutions have been developed. These digital applications allow users to communicate with physicians via novel distribution channels, creating a more efficient and cohesive method for accessing data critically in emergent situations; however, rapid growth in these technologies has also permitted the potential for misinformation and miscommunication between parties. A critical approach is necessary in evaluating the information provided by these various services.

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